112539

U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office

8/8

SEARCH REQUEST FORM

Requestor's Name: R GITOMER

Serial Number: 09/971,852

Date: 1/21/04

Phone: 272-0916

Art Unit: 1651

Search Topic:

Please write a detailed statement of search topic. Describe specifically as possible the subject matter to be searched. Define any terms that may have a special meaning. Give examples or relevent citations, authors, keywords, etc., if known. For sequences, please attach a copy of the sequence. You may include a copy of the broadest and/or most relevent claim(s).

69630

3D6S

(STIC)

STAFF USE ONLY

Date completed: 1/29/04

Searcher: Arnold Schulwitz

Terminal time: _____

Elapsed time: _____

CPU time: _____

Total time: _____

Number of Searches: _____

Number of Databases: _____

Search Site

_____ STIC

_____ CM-1

_____ Pre-S

Type f Search

_____ N.A. Sequence

_____ A.A. Sequence

_____ Structure

_____ Bibliographic

Vendors

_____ IG

_____ STN

_____ Dialog

_____ APS

_____ Geninfo

_____ SDC

_____ DARC/Questel

_____ Other

PTO-1590 (9-60)

STIC Search Report
Biotech-Chem Library

STIC Database Tracking Number: 112539

TO: Ralph J Gitomer
Location: REM-3D65
Art Unit: 1651
Thursday, January 29, 2004

Case Serial Number: 09/971852

From: Deirdre Arnold
Location: Biotech-Chem Library
~~CM1-6B01~~ Rem 1 A64
Phone: ~~305-8682~~ 571-272-2532

Deirdre.arnold@uspto.gov

Search Notes

This search was supervised by Paul Schulwitz.

Note that duplicates may exist between the HCAPLUS results (packets 1 and 2) and the results for searches in Medline, Embase, and Biosis (packet 3).

Thank you for using STIC services.

Regards,
Deirdre Arnold

Search and Information Resources Administration

STIC SEARCH RESULTS FEEDBACK FORM

Biotech-Chem Library

Questions about the scope or the results of the search? Contact ***the searcher or contact:***

Mary Hale, Information Branch Supervisor
Remsen Bldg. 01 D86
571-272-2507

Voluntary Results Feedback Form

- *I am an examiner in Workgroup:* ☐ *Example: 1610*

- *Relevant prior art **found**, search results used as follows:*

  - ☐ 102 rejection
  - ☐ 103 rejection
  - ☐ Cited as being of interest.
  - ☐ Helped examiner better understand the invention.
  - ☐ Helped examiner better understand the state of the art in their technology.

  Types of relevant prior art found:

  - ☐ Foreign Patent(s)
  - ☐ Non-Patent Literature
    (journal articles, conference proceedings, new product announcements etc.)

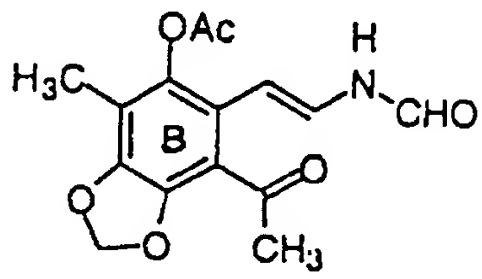
- *Relevant prior art **not found:***

  - ☐ Results verified the lack of relevant prior art (helped determine patentability).
  - ☐ Results were not useful in determining patentability or understanding the invention.

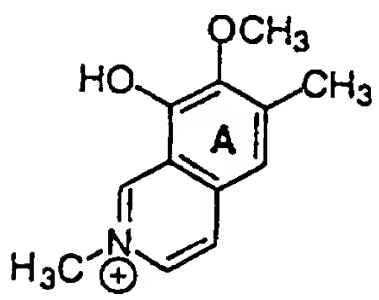
Comments:

Drop off or send completed forms to STIC Biotech Chem Library Remsen Bldg

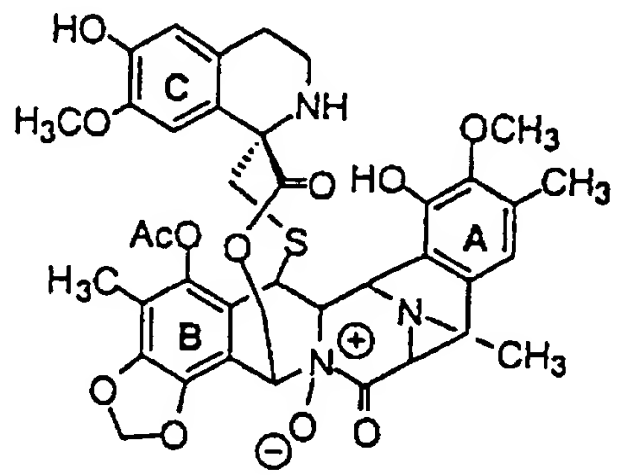
17. Metabolites of Ecteinascidin 743 formed by human cytochrome CYP3A4, said metabolites being selected from the group consisting of:



ETM 305



ETM 204



ETM 775

MOST PREFERRED SPECIES

18. The Ecteinascidin 743 metabolite of Claim 17, designated herein as ETM-305.

19. The Ecteinascidin 743 metabolite of Claim 17, designated herein as ETM-204.

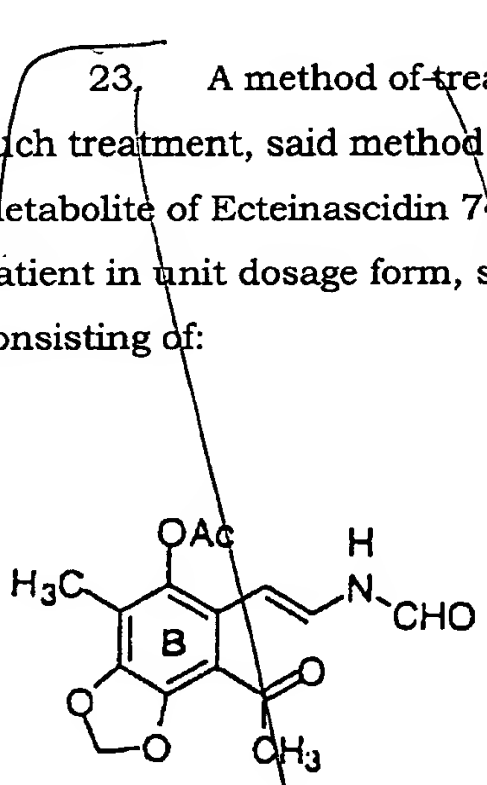
20. A pharmaceutical composition comprising one or more of the Eceteinascidin 743 metabolites of Claim 17 and a pharmaceutically acceptable diluent, excipient or carrier.

21. The pharmaceutical composition of Claim 20, wherein the

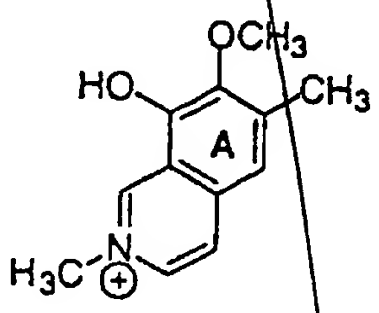
Ecteinascidin 743 metabolite is designated herein as ETM-305.

22. The pharmaceutical composition of Claim 20, wherein the Ecteinascidin 743 metabolite is designated herein as ETM-204.

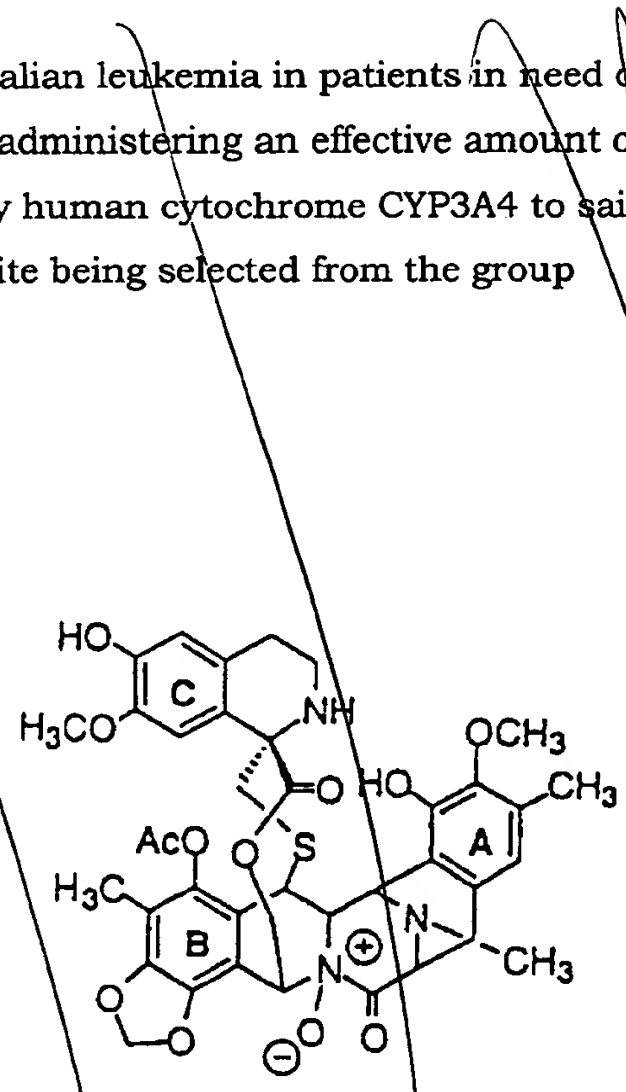
23. A method of treating mammalian leukemia in patients in need of such treatment, said method comprising administering an effective amount of a metabolite of Ecteinascidin 743 formed by human cytochrome CYP3A4 to said patient in unit dosage form, said metabolite being selected from the group consisting of:



ETM 305



ETM 204



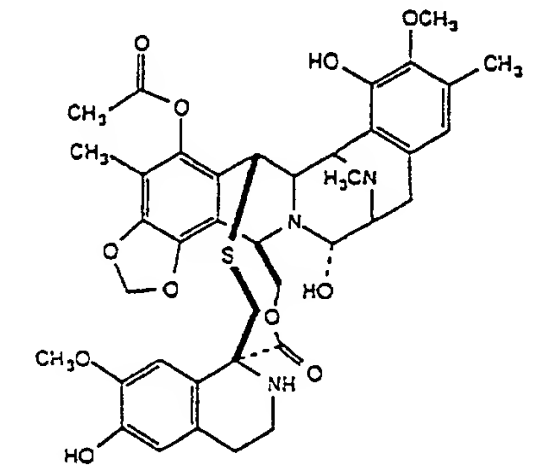
ETM 775

or mixtures thereof.

24. The method of claim 23, wherein the Ecteinascidin 743 metabolite is designated herein as ETM-305.

Goldwasser et al., *Proceedings of the American Association for Cancer Research*, **39**: 598 (1998); Kuffel et al., *Proceedings of the American Association for Cancer Research*, **38**: 596 (1997); Moore et al., *Proceedings of the American Association for Cancer Research*, **38**: 314 (1997); Mirsalis et al., *Proceedings of the American Association for Cancer Research*, **38**: 309 (1997); Reid et al., *Cancer Chemotherapy and Pharmacology*, **38**: 329-334 (1996); Faircloth et al., *European Journal of Cancer*, **32A**, Supp. 1, pp. S5 (1996); Garcia-Rocha et al., *British Journal of Cancer*, **73**: 875-883 (1996); Eckhardt et al., *Proceedings of the American Association for Cancer Research*, **37**: 409 (1996); Hendriks et al., *Proceedings of the American Association for Cancer Research*, **37**: 389 (1996); the disclosures of which are hereby incorporated herein by reference.

Ecteinascidin 743 (Et 743) has the following structure:



Et 743

In view of the impressive antitumor activities of this class of compounds, the search continues for related structures that may possess equal or higher levels of antitumor activity. The present invention, which is directed to the isolation and characterization of natural metabolites of Et 743, is a result of these continued studies.

```
=> file stnguide

FILE 'STNGUIDE' ENTERED AT 10:54:14 ON 29 JAN 2004
USE IS SUBJECT TO THE TERMS OF YOUR CUSTOMER AGREEMENT
COPYRIGHT (C) 2004 AMERICAN CHEMICAL SOCIETY, JAPAN SCIENCE
AND TECHNOLOGY CORPORATION, AND FACHINFORMATIONSZENTRUM KARLSRUHE

FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Jan 23, 2004 (20040123/UP).

=> file registry

FILE 'REGISTRY' ENTERED AT 10:54:20 ON 29 JAN 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2004 American Chemical Society (ACS)

Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:   28 JAN 2004  HIGHEST RN 642928-00-5
DICTIONARY FILE UPDATES:  28 JAN 2004  HIGHEST RN 642928-00-5

TSCA INFORMATION NOW CURRENT THROUGH JULY 14, 2003

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

=> file hcaplus

FILE 'HCAPLUS' ENTERED AT 10:54:30 ON 29 JAN 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2004 AMERICAN CHEMICAL SOCIETY (ACS)

Copyright of the articles to which records in this database refer is
held by the publishers listed in the PUBLISHER (PB) field (available
for records published or updated in Chemical Abstracts after December
26, 1996), unless otherwise indicated in the original publications.
The CA Lexicon is the copyrighted intellectual property of the
the American Chemical Society and is provided to assist you in searching
databases on STN.  Any dissemination, distribution, copying, or storing
of this information, without the prior written consent of CAS, is
strictly prohibited.

FILE COVERS 1907 - 29 Jan 2004  VOL 140 ISS 5
FILE LAST UPDATED: 28 Jan 2004  (20040128/ED)

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.
```

Headings for files used.

=> file caplus

FILE 'CAPLUS' ENTERED AT 10:55:54 ON 29 JAN 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

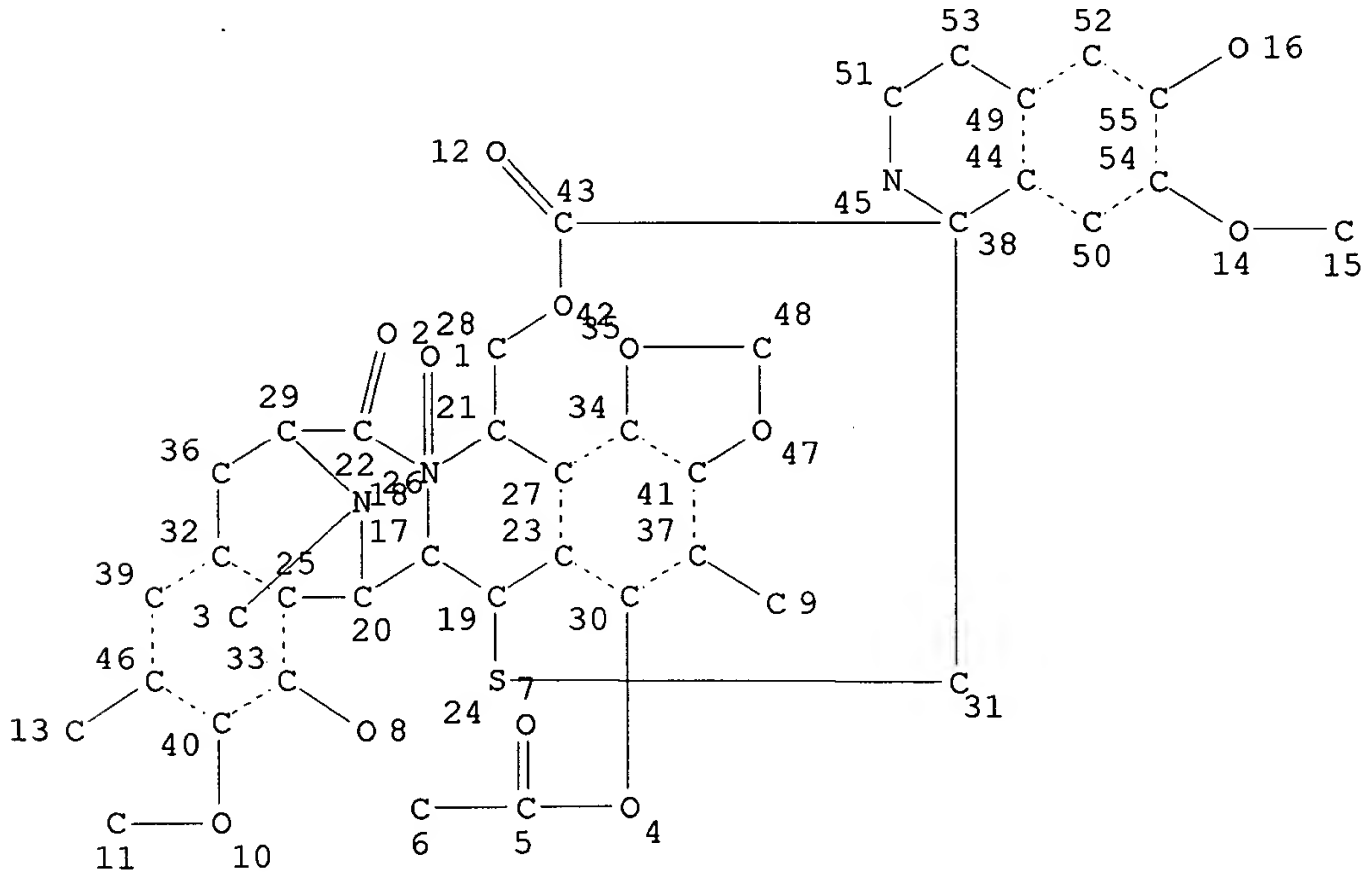
FILE COVERS 1907 - 29 Jan 2004 VOL 140 ISS 5
FILE LAST UPDATED: 28 Jan 2004 (20040128/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> FIL STNGUIDE

=> d que l21
L2 STR

ETM775



NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

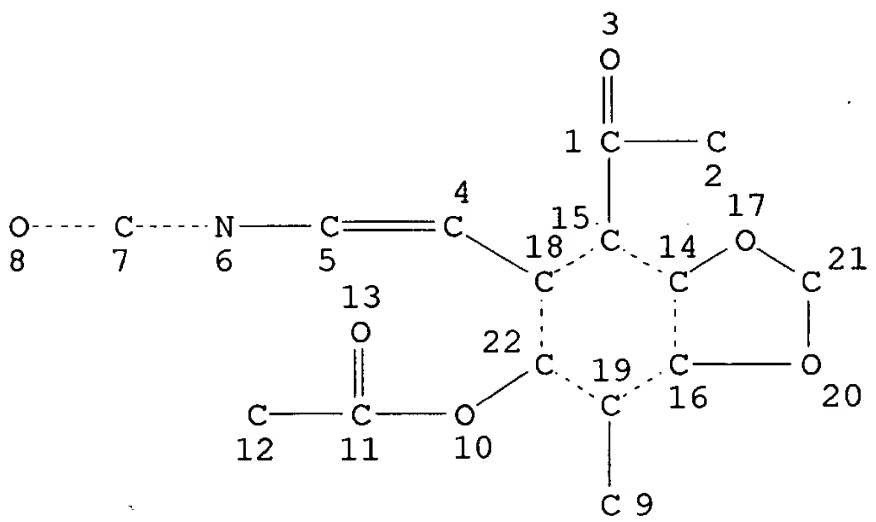
GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 55

STEREO ATTRIBUTES: NONE
L3 1 SEA FILE=REGISTRY FAM FUL L2
L4 1 SEA FILE=REGISTRY ABB=ON PLU=ON 215035-11-3/RN
L5 1 SEA FILE=REGISTRY ABB=ON PLU=ON L3 OR L4
L21 3 SEA FILE=HCAPLUS ABB=ON PLU=ON L5

Family search: finds exact substance and any multicomponent substances containing it.

search for references in HCAPLUS

=> d que l22
L6 STR



ETM305

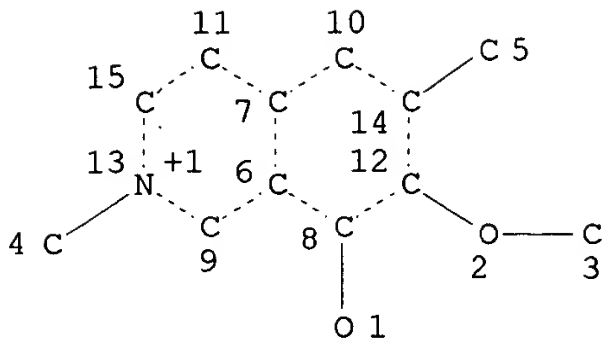
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 22

STEREO ATTRIBUTES: NONE
L7 1 SEA FILE=REGISTRY FAM FUL L6
L8 1 SEA FILE=REGISTRY ABB=ON PLU=ON 250159-76-3/RN
L9 1 SEA FILE=REGISTRY ABB=ON PLU=ON L7 OR L8
L22 2 SEA FILE=HCAPLUS ABB=ON PLU=ON L9

search for references in HCAPLUS

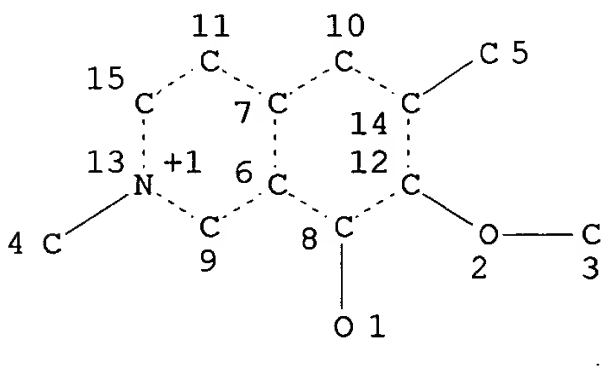
=> d que l23
L10 STR



NODE ATTRIBUTES:
CHARGE IS E+1 AT 13
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 15

STEREO ATTRIBUTES: NONE
L11 1 SEA FILE=REGISTRY EXA FUL L10 STM 204
L12 STR



NODE ATTRIBUTES:
CHARGE IS E+1 AT 13
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 15

STEREO ATTRIBUTES: NONE
L13 1 SEA FILE=REGISTRY EXA FUL L12
L14 1 SEA FILE=REGISTRY ABB=ON PLU=ON L11 OR L13
L23 2 SEA FILE=HCAPLUS ABB=ON PLU=ON L14 search for references in HCAPLUS

=> d l26 ibib hitstr abs
YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS' - CONTINUE? (Y)/N:y
* Display all references without duplicates. *

L26 ANSWER 1 OF 3 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:800791 HCAPLUS
DOCUMENT NUMBER: 136:160824

TITLE: Search for metabolites of ecteinascidin 743, a novel, marine-derived, anti-cancer agent, in man

AUTHOR(S): Sparidans, Rolf W.; Rosing, Hilde; Hillebrand, Michel J. X.; Lopez-Lazaro, Luis; Jimeno, Jose M.; Manzanares, Ignacio; Van Kesteren, Charlotte; Cvitkovic, Esteban; Van Oosterom, Alan T.; Schellens, Jan H. M.; Beijnen, Jos H.

CORPORATE SOURCE: Faculty of Pharmacy, Department of Biomedical Analysis, Division of Drug Toxicology, Utrecht University, Utrecht, 3584 CA, Neth.

SOURCE: Anti-Cancer Drugs (2001), 12(8), 653-666
CODEN: ANTDEV; ISSN: 0959-4973

PUBLISHER: Lippincott Williams & Wilkins

DOCUMENT TYPE: Journal

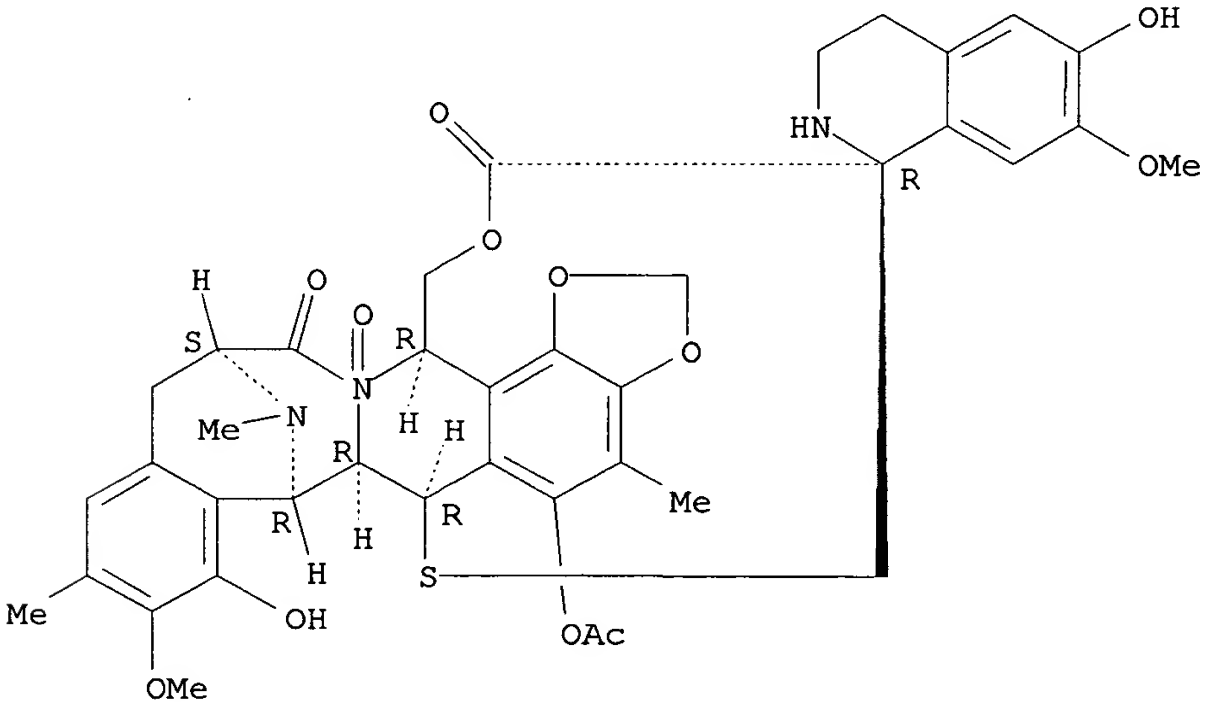
LANGUAGE: English

IT **215035-11-3**, ETM 775 **250159-76-3 250159-77-4**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(metabolites of antitumor drug ecteinascidin 743 in man)

RN 215035-11-3 HCAPLUS

CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-14H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinoline]-14,19-dione, 5-(acetyloxy)-3',4',6,6a,7,12,13,16-octahydro-6',8-dihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, 15-oxide, (1'R,6R,6aR,7R,13S,16R)- (9CI) (CA INDEX NAME)

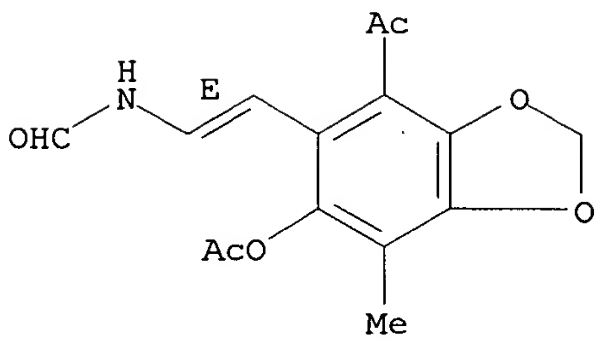
Absolute stereochemistry.
Currently available stereo shown.



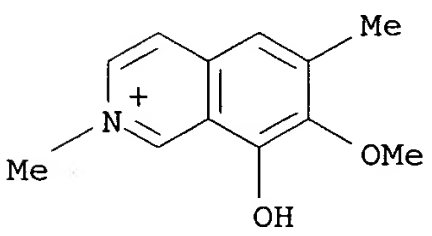
RN 250159-76-3 HCAPLUS

CN Formamide, N-[(1E)-2-[4-acetyl-6-(acetyloxy)-7-methyl-1,3-benzodioxol-5-yl]ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



RN 250159-77-4 HCAPLUS
CN Isoquinolinium, 8-hydroxy-7-methoxy-2,6-dimethyl- (9CI) (CA INDEX NAME)



AB Ecteinascidin 743 (ET-743) is a potent anti-tumoral agent of a marine origin. It is currently being tested in phase II clin. trials using a 3-weekly 24-h i.v. infusion of 1500 μg/m2 and 3-h infusions of 1650 μg/m2. Knowledge of the metabolism of ET-743 is, however, still scarce. In the present study, a qual. chromatog. discovery of metabolites of ET-743 in man is reported. ET-743 and its demethylated analog ET-729 were incubated at 37 in the presence of enzyme systems, pooled human microsomes, pooled human plasma and uridine 5'-diphosphoglucuronyltransferase, resp., in appropriate media. Reaction products were investigated chromatog. using photodiode array and ion spray-mass spectrometric detection (LC-MS). The main reaction products in microsomal incubations of ET-743 resulted from a remarkable breakdown of the mol. In plasma the drugs were deacetylated, and the transferase did actually yield a glucuronide of both ET-743 and ET-729. In contrast, screening of urine, plasma and bile, collected from patients treated with ET-743 at the highest dose levels, using a sensitive LC-MS assay, did not result in detection of ET-729 and metabolites which were generated in vitro. The urinary excretion of ET-743 in man was lower than 0.7% of the administered dose for a 24-h infusion.

REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> => d l26 ibib hitstr abs 2-3
YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS' - CONTINUE? (Y)/N:y

L26 ANSWER 2 OF 3 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:736474 HCAPLUS
DOCUMENT NUMBER: 131:332115
TITLE: Metabolites of ecteinascidin 743 as antitumor agents
INVENTOR(S): Rinehart, Kenneth L.; Morales, Jose J.; Reid, Joel; Reymundo, Isabel; Floriano, Pablo; Garcia Gravalos, Lola
PATENT ASSIGNEE(S): Pharma Mar, S.A., Spain

SOURCE: PCT Int. Appl., 44 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9958125	A1	19991118	WO 1999-US10233	19990511
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2331593	AA	19991118	CA 1999-2331593	19990511
AU 9940737	A1	19991129	AU 1999-40737	19990511
AU 759281	B2	20030410		
BR 9910419	A	20010109	BR 1999-10419	19990511
EP 1077698	A1	20010228	EP 1999-924169	19990511
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
US 6316214	B1	20011113	US 1999-309947	19990511
JP 2002514597	T2	20020521	JP 2000-547976	19990511
NZ 508585	A	20021126	NZ 1999-508585	19990511
NO 2000005671	A	20010110	NO 2000-5671	20001110
BG 105023	A	20010831	BG 2000-105023	20001205
US 2002032326	A1	20020314	US 2001-971852	20011003

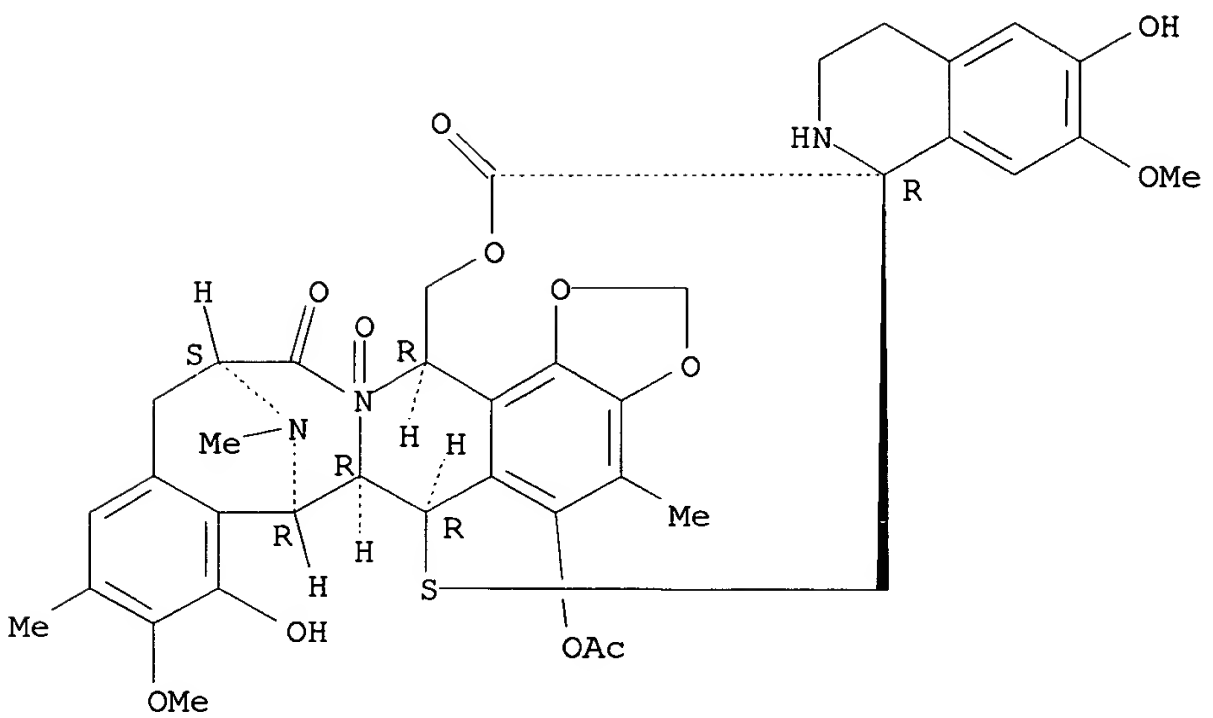
PRIORITY APPLN. INFO.:
US 1998-85024P P 19980511
US 1999-309947 A1 19990511
WO 1999-US10233 W 19990511

IT **215035-11-3**, ETM 775 **250159-76-3**, ETM 305
250159-77-4, ETM 204
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); OCCU (Occurrence); USES (Uses)
(metabolites of ecteinascidin 743 as antitumor agents)

RN 215035-11-3 HCAPLUS

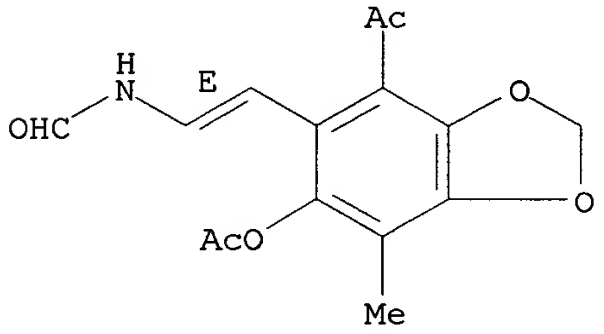
CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-14H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinoline]-14,19-dione, 5-(acetyloxy)-3',4',6,6a,7,12,13,16-octahydro-6',8-dihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, 15-oxide, (1'R,6R,6aR,7R,13S,16R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Currently available stereo shown.

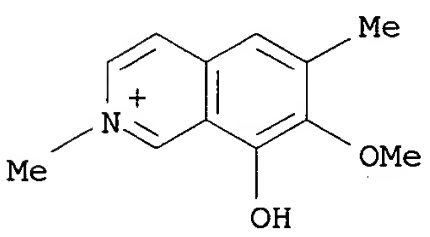


RN 250159-76-3 HCAPLUS
CN Formamide, N-[(1E)-2-[4-acetyl-6-(acetyloxy)-7-methyl-1,3-benzodioxol-5-yl]ethenyl]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



RN 250159-77-4 HCAPLUS
CN Isoquinolinium, 8-hydroxy-7-methoxy-2,6-dimethyl- (9CI) (CA INDEX NAME)



AB The purification and structure elucidation of several products of the metabolism of
ecteinascidin 743 by human cytochrome CYP3A4 have been accomplished. These compds. are abbreviated herein as "ETM" followed by a numeric value which represents the approx. mol. weight The structures of these ecteinascidin metabolites, e.g. ETM 305, ETM 204 and ETM 775 are elucidated. ET 743 was incubated with human lymphoblast-expressed CYP3A4

isoform containing an NADPH generating system. After 4 h at 37° the reaction was stopped with ice cold acetonitrile and the supernatants were separated and above ecteinascidins were isolated and purified. ETM 305 and ETM 775 had antitumor activity against murine leukemia, human lung carcinoma, and human malignant melanoma cell lines.

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 3 OF 3 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:706050 HCAPLUS
DOCUMENT NUMBER: 129:326085
TITLE: Nucleophile substituted ecteinascidins and N-oxide ecteinascidins from Ecteinascidia turbinata for tumor treatment, and pharmaceutical and veterinary compositions
INVENTOR(S): Rinehart, Kenneth L.; Zhou, Tong
PATENT ASSIGNEE(S): The Board of Trustees of the University of Illinois, USA
SOURCE: PCT Int. Appl., 27 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

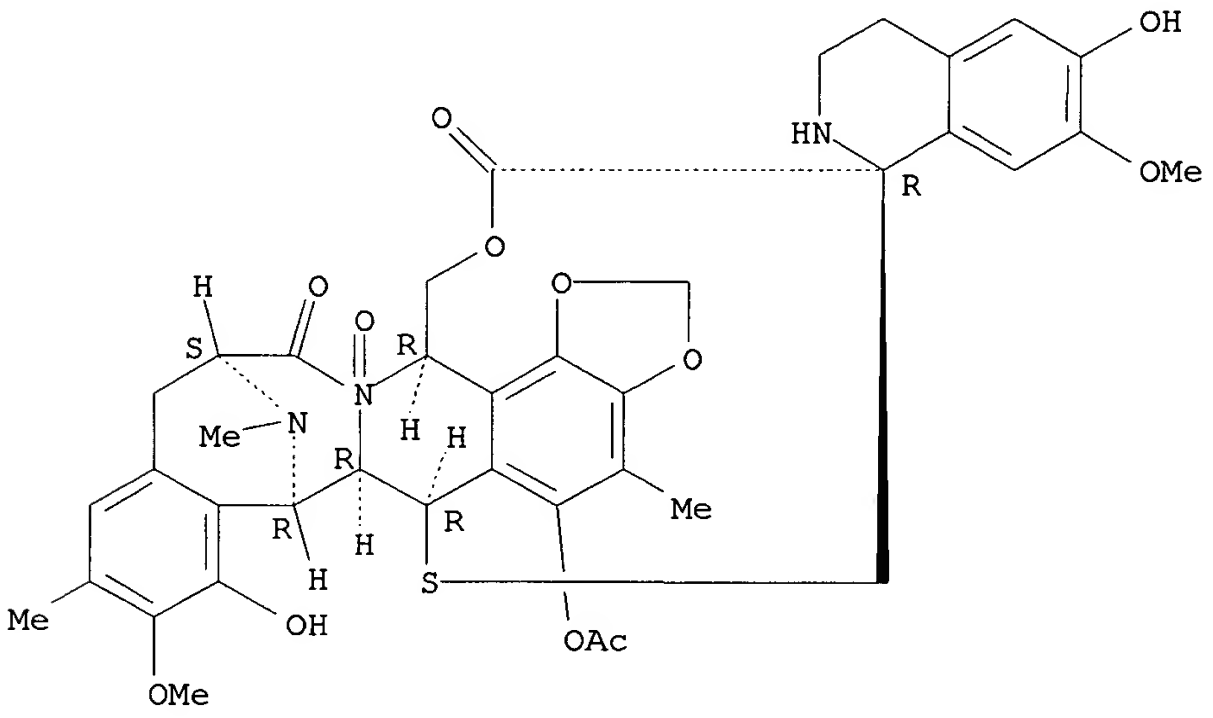
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9846080	A1	19981022	WO 1998-US7340	19980414
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5985876	A	19991116	US 1998-58499	19980410
AU 9871114	A1	19981111	AU 1998-71114	19980414
AU 747303	B2	20020616		
EP 975218	A1	20000202	EP 1998-918132	19980414
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
BR 9808588	A	20000523	BR 1998-8588	19980414
JP 2001523228	T2	20011120	JP 1998-544140	19980414
NO 9905016	A	19991210	NO 1999-5016	19991014
MX 9909503	A	20000831	MX 1999-9503	19991015

PRIORITY APPLN. INFO.: US 1997-43596P P 19970415
WO 1998-US7340 W 19980414

IT **215035-11-3P**, Ecteinascidin 775
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(nucleophile substituted ecteinascidins and N-oxide ecteinascidins from Ecteinascidia turbinata for tumor treatment, and pharmaceutical and veterinary compns.)
RN 215035-11-3 HCAPLUS
CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-14H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinoline]-14,19-

dione, 5-(acetyloxy)-3',4',6,6a,7,12,13,16-octahydro-6',8-dihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, 15-oxide, (1'R,6R,6aR,7R,13S,16R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Currently available stereo shown.

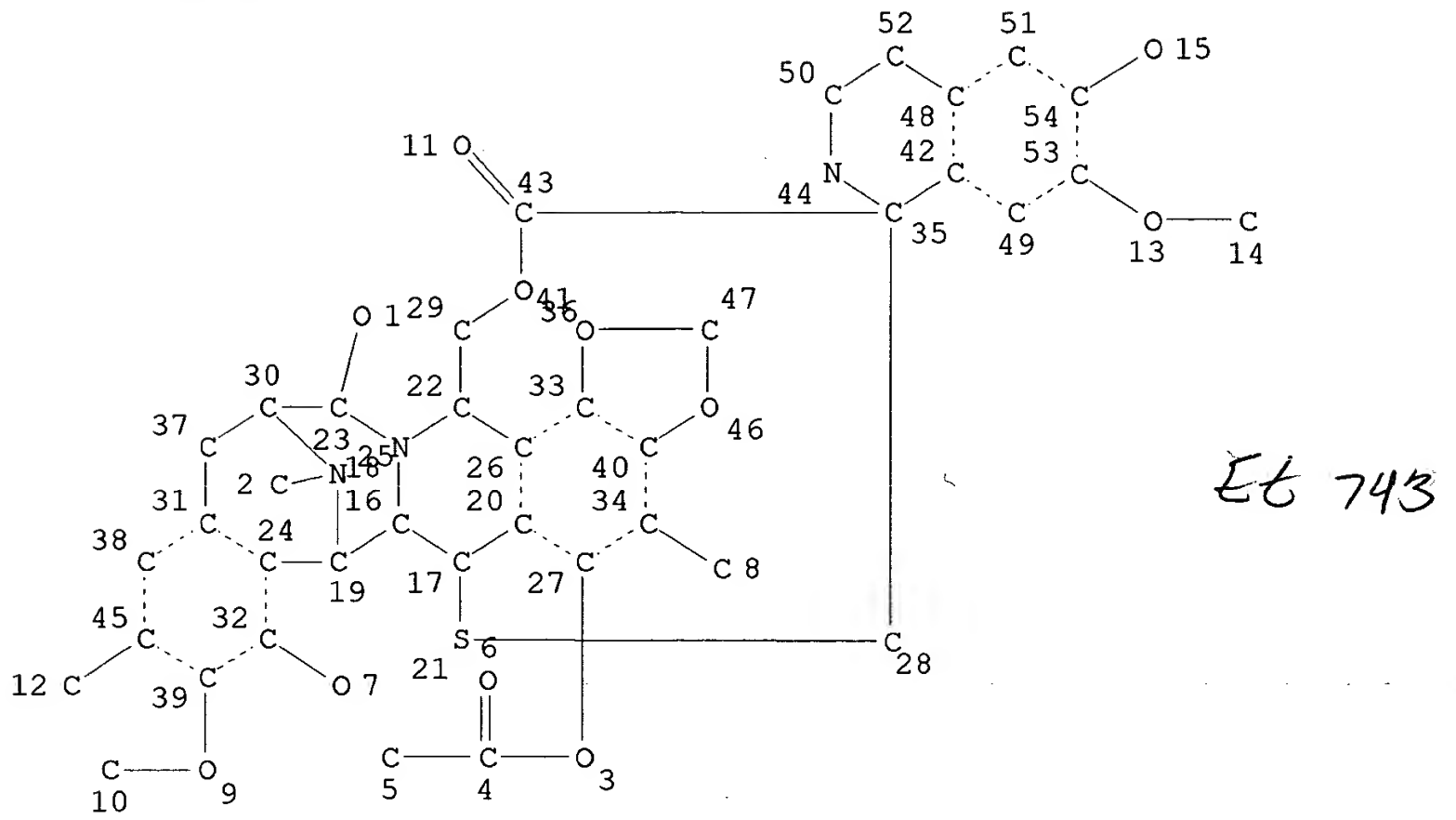


AB Five new nucleophile substituted ecteinascidin (Et) compds. have been isolated from exts. of Ecteinascidia turbinata. These compds. have been purified by chromatog. techniques and their structures and bioactivities have been determined The five nucleophile substituted Et compds. have been designated herein as Et 802, Et 788, Et 760, Et 858, and Et 815. Also obtained were three new N-oxide ecteinascidin compds., which have been designated herein as Et 717, Et 775, and Et 789. Some of these newly discovered Et compds. show exceedingly potent cytotoxicity against L1210.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d que l25
L15 STR

L15 str

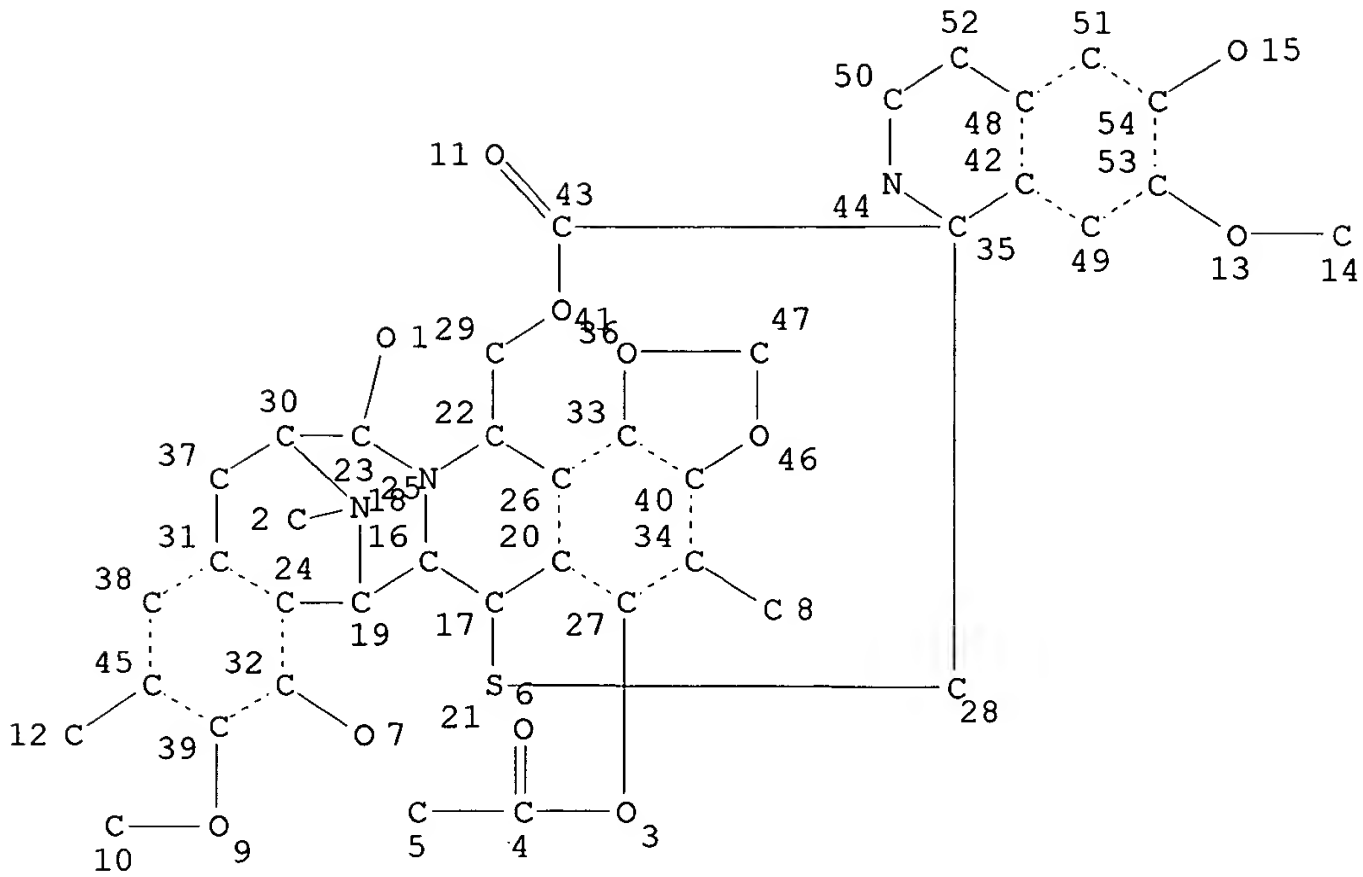


Et 743

NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 54

STEREO ATTRIBUTES: NONE
L16 4 SEA FILE=REGISTRY FAM FUL L15
L17 STR



NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 54

STEREO ATTRIBUTES: NONE
L18 2 SEA FILE=REGISTRY EXA FUL L17
L19 4 SEA FILE=REGISTRY ABB=ON PLU=ON L16 OR L18
L24 132 SEA FILE=HCAPLUS ABB=ON PLU=ON L19
L25 79 SEA FILE=HCAPLUS ABB=ON PLU=ON L24 AND PY<2002

search for References in HCAPLUS

limit by publication year <2002

=> d l27 ibib hitstr abs 1-
YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS' - CONTINUE? (Y)/N:y

* Display all references not included in previous results. *

YOU HAVE REQUESTED DATA FROM 76 ANSWERS - CONTINUE? Y/(N):y

L27 ANSWER 1 OF 76 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:375129 HCAPLUS
DOCUMENT NUMBER: 137:379518
TITLE: The antitumor agent ecteinascidin 743: Characterization of its covalent DNA adducts and chemical stability
AUTHOR(S): Hurley, Laurence H.; Zewail-Foote, Maha
CORPORATE SOURCE: The University of Arizona Cancer Center, Tucson, AZ, 85724, USA

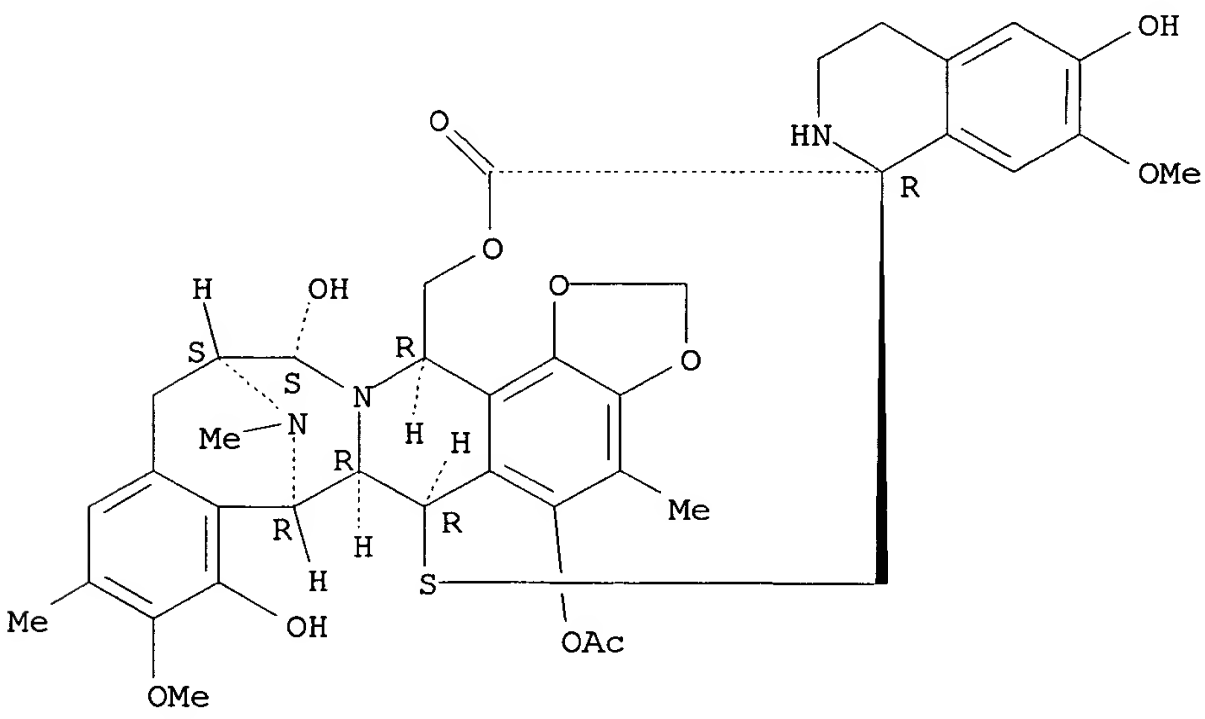
SOURCE: Advances in Experimental Medicine and Biology (**2001**), 500(Biological Reactive Intermediates VI), 289-299
CODEN: AEMBAP; ISSN: 0065-2598
PUBLISHER: Kluwer Academic/Plenum Publishers
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

IT **114899-77-3**, Ecteinascidin 743
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(characterization of ecteinascidin 743 covalent DNA adducts and chemical stability as an antitumor agent)

RN 114899-77-3 HCAPLUS

CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



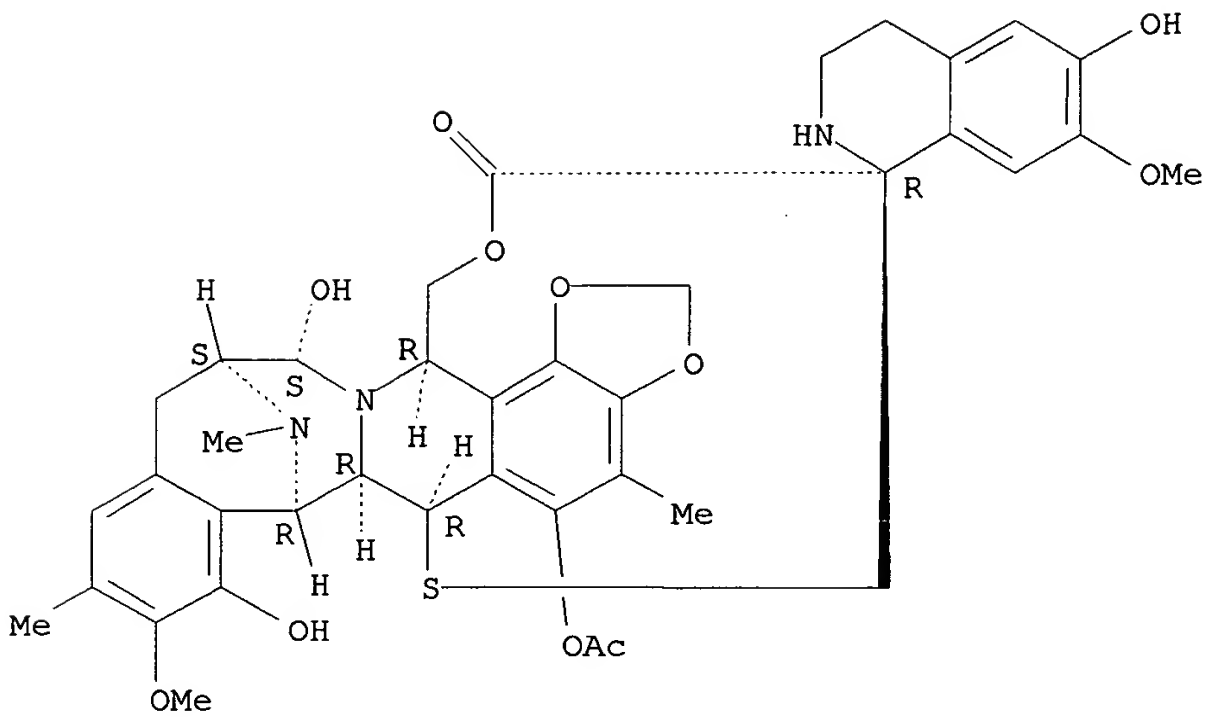
AB A review. Ecteinascidin 743 (Et 743), a natural product derived from the Caribbean tunicate Eteinascidia turbinata, is a potent antitumor agent currently in phase II clin. trials. Et 743 binds in the minor groove of DNA, forming covalent adducts by reacting with N2 of guanine. Although DNA is considered to be the macromol. receptor for Et 743, the precise mechanism by which Et 743 exerts its remarkable antitumor activity has not yet been elucidated. The aim of this study is to provide a rationale for the antitumor activity of Et 743 by studying its fundamental interactions with DNA at the mol. level. First, DNA structural distortions induced by Et 743 were characterized using gel electrophoresis. Surprisingly, Et 743 bends DNA toward the major groove, a unique feature among DNA-interactive agents that occupy the minor groove. Second, in order to gain further insight into the mol. basis behind the apparent sequence selectivity of Et 743, the stability and structure of Et 743 adducts at different target sequences were determined On the basis of this data, the overall stability of the Et 743-DNA adducts was found to be governed by the DNA target

sequence, where the inability of Et 743 to form optimum bonding networks with its optimum recognition sites leads to the formation of an unstable adduct. Consequently, the reaction of Et 743 with DNA is reversible, and the rate of the reverse reaction is a function of the target and flanking sequences. The results from this study demonstrate that Et 743 differs from other DNA alkylating agents by its effects on DNA structure and sequence-dependent chemical stability. This information provides important insight into the underlying mechanisms for its unique profile of antitumor activity.

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 2 OF 76 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:2520 HCAPLUS
DOCUMENT NUMBER: 137:15374
TITLE: Antitumor activity- and gene expression-based profiling of ecteinascidin Et 743 and phthalascidin Pt 650
AUTHOR(S): Martinez, Eduardo J.; Corey, E. J.; Owa, Takashi
CORPORATE SOURCE: Department of Chemistry and Chemical Biology, Harvard University, Cambridge, MA, 02138, USA
SOURCE: Chemistry & Biology (**2001**), 8(12), 1151-1160
CODEN: CBOLE2; ISSN: 1074-5521
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **114899-77-3**, Et743
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antitumor activity- and gene expression-based profiling of ecteinascidin Et 743 and phthalascidin Pt 650)
RN 114899-77-3 HCAPLUS
CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



AB Ecteinascidin 743 (Et 743) is a potent antitumor marine alkaloid currently undergoing phase II clin. trials. The synthetic analog phthalascidin (Pt 650), a designed structural analog of Et 743 displays in vitro potency comparable to Et 743. In this study, we used a panel of 36 human cancer cell lines, flow cytometry and oligonucleotide microarrays to analyze further these two compds. in a parallel fashion with regard to both antitumor activity (phenotype) and gene expression (genotype) bases. The cancer panel experiment established that activity patterns of Et 743 and Pt 650 were essentially the same with their IC values ranging from pM to low nM. By means of flow cytometric cell cycle anal. using HCT116 cells, they were shown to disrupt S phase progression after a 12-h treatment at 2.0 nM, eventually resulting in the late S and G2/M accumulation at the 24-h time point. Array-based gene expression monitoring also demonstrated that the Et 743 and Pt 650 profiles were highly similar in two distinct cancer cell lines, HCT116 colon and MDA-MB-435 breast. Characteristic changes were observed in subsets of genes involved in DNA damage response, transcription and signal transduction. In HCT116 carrying the wild-type p53 tumor suppressor gene, the up-regulation of several p53-responsive genes was evident. Furthermore, a subset of genes encoding DNA-binding proteins to specific promoter regions (e.g. the CCAAT box) was down-regulated in both cell lines, suggesting one potential mode of action of this series of antitumor agents. A combination of gene expression anal. using oligonucleotide microarrays and flow cytometry confirms an earlier finding that Et 743 and Pt 650 have remarkably similar biol. activities.

REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 3 OF 76 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:926251 HCAPLUS
DOCUMENT NUMBER: 136:209908
TITLE: ET-743 pharmamar/NCI/Ortho Biotech
AUTHOR(S): Verschraegen, Claire F.; Glover, Katrina
CORPORATE SOURCE: MD Anderson Cancer Center, University of Texas, Houston, TX, 77030, USA
SOURCE: Current Opinion in Investigational Drugs (PharmaPress Ltd.) (**2001**), 2(11), 1631-1638

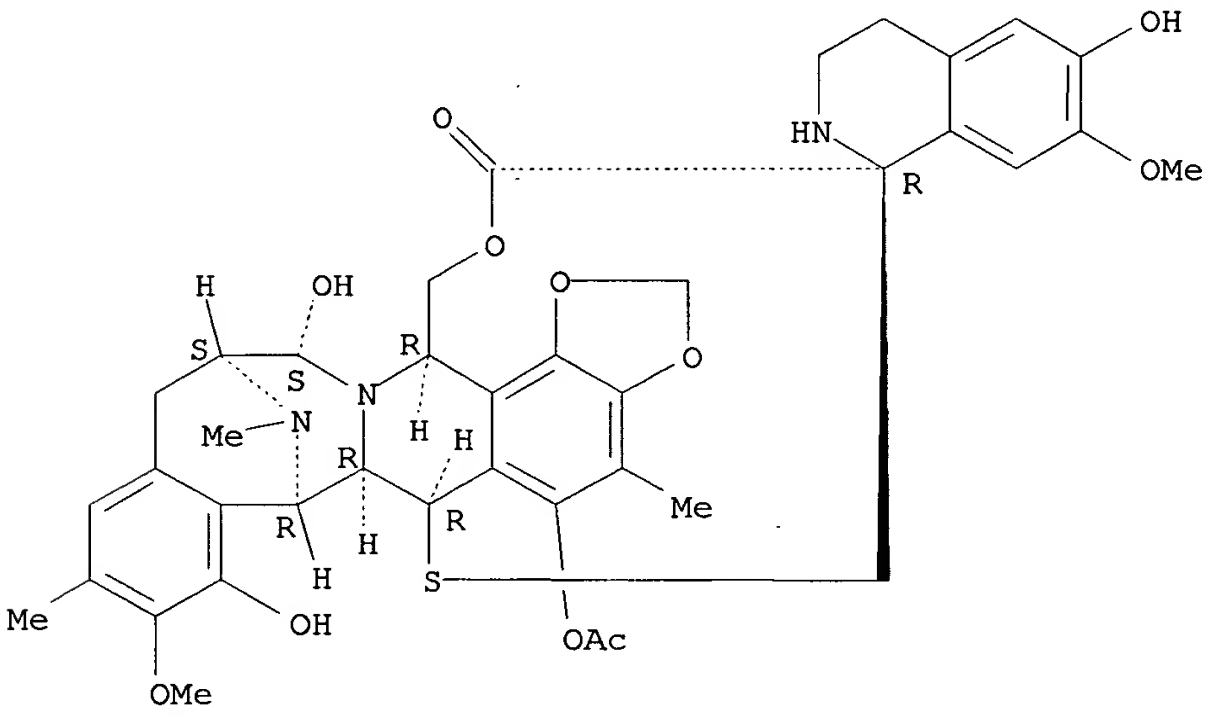
CODEN: COIDAZ
PUBLISHER: PharmaPress Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

IT **114899-77-3**, Et 743
RL: ADV (Adverse effect, including toxicity); DMA (Drug mechanism of action); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ET-743 as a potential treatment for several tumor types including breast cancer, lung cancer, ovarian cancer and melanoma)

RN 114899-77-3 HCAPLUS

CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



AB A review. Exteinascidin-743 (ET-743), a tetrahydroisoquinoline alkaloid isolated from the Caribbean tunicate, Ecteinascidia turbinata, is under development by PharmaMar (the pharmaceutical subsidiary of Zeltia), the National Cancer Institute (NCI) and Ortho Biotech, as a potential treatment for several tumor types including breast cancer, lung cancer, ovarian cancer and melanoma. It appears to function by DNA minor groove alkylation, which induces topoisomerase I-mediated protein-linked DNA strand breakage. ET-743 is an analog of ET-729. As of Feb. 1999, it was in phase II trials, and, in August 2001, PharmaMar expected phase II trials for breast, ovarian and non-small cell lung cancer to be completed by August 2002. In June 2001, the EMEA awarded ET-743 Orphan Drug status for the treatment of soft tissue sarcoma. The orphan medicinal product designation is designed to expedite the registration of pharmaceuticals for life-threatening or debilitating conditions with low prevalence (< 5 per 10,000 in the EU), for which no satisfactory treatment exists. The designation offers the sponsor several incentives, such as centralized procedure review of the Marketing Authorization Application and, upon approval, ten-year marketing exclusivity throughout Europe for the

therapeutic indication for which it was granted. Pharma Mar is also collaborating with the European Organization for Research and Treatment of Cancer (EORTC); Pharma Mar has obtained the worldwide rights to ET-743, amongst other ecteinascidins, from the University of Illinois. In August 2001, Dresdner Kleinwort Wasserstein predicted total sales, for all ET-743's indications, of $1 million in 2002, rising through $1106 million in 2007 to $2725 million in 2011.

REFERENCE COUNT: 70 THERE ARE 70 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

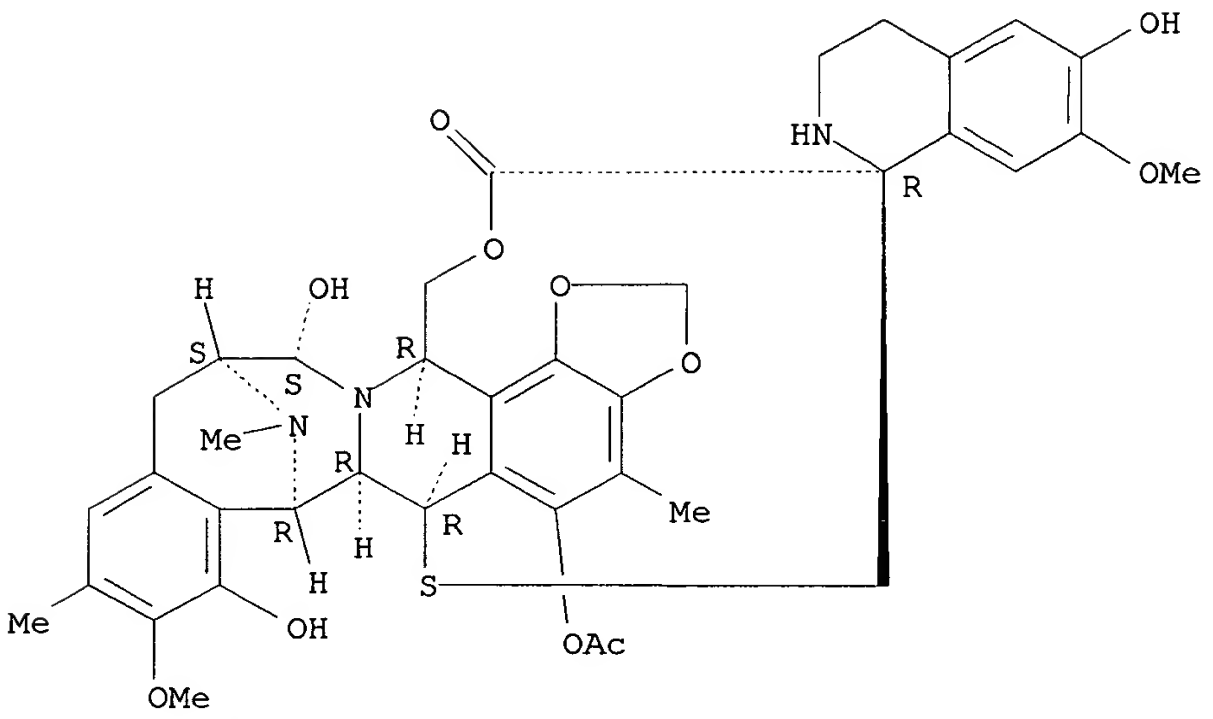
L27 ANSWER 4 OF 76 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:924096 HCAPLUS
DOCUMENT NUMBER: 136:31648
TITLE: Toxicity typing using liver stem cells
INVENTOR(S): Snodgrass, H. Ralph
PATENT ASSIGNEE(S): Vistagen, Inc., USA
SOURCE: PCT Int. Appl., 73 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001096866	A1	20011220	WO 2001-US19187	20010614 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2002012905	A1	20020131	US 2001-881526	20010614
EP 1290444	A1	20030312	EP 2001-946391	20010614
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				

PRIORITY APPLN. INFO.: US 2000-211606P P 20000614
WO 2001-US19187 W 20010614

IT **114899-77-3**, Ecteinascidin 743
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(toxicity typing using liver stem cells)
RN 114899-77-3 HCAPLUS
CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



AB The invention provides methods and systems for identifying and typing toxicity of chemical compns., as well as for screening new compns. for toxicity. The invention involves detecting alterations in gene or protein expression and hence establishing mol. profiles in isolated mammalian LSCs contacted with various chemical compns. of known and unknown toxicities, and correlating the mol. profiles with toxicities of the chemical compns. Application to e.g. screening of anticancer drugs for tissue and organ toxicities is described.

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 5 OF 76 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:924095 HCAPLUS
DOCUMENT NUMBER: 136:31647
TITLE: Toxicity typing using mesenchymal stem cells
INVENTOR(S): Snodgrass, H. Ralph
PATENT ASSIGNEE(S): Vistagen, Inc., USA
SOURCE: PCT Int. Appl., 67 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

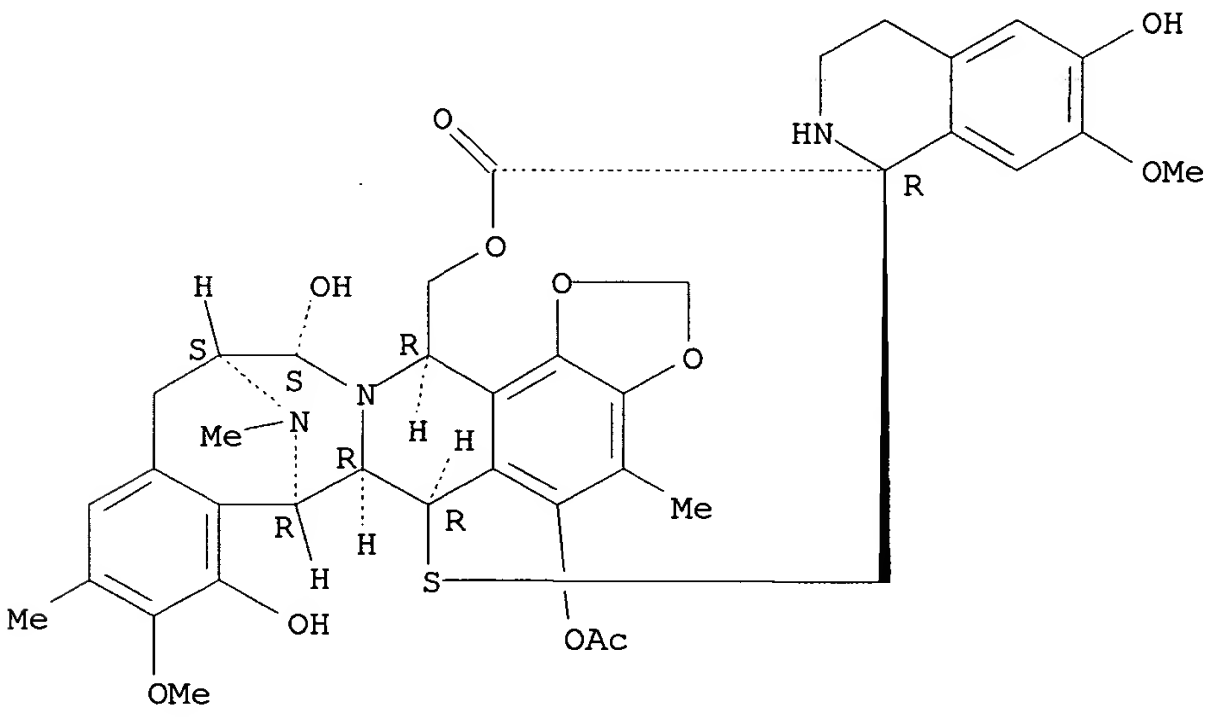
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001096865	A1	20011220	WO 2001-US19048	20010614 <--

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

US 2002045179 A1 20020418 US 2001-881475 20010614
EP 1290443 A1 20030312 EP 2001-946335 20010614
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR
PRIORITY APPLN. INFO.: US 2000-211608P P 20000614
WO 2001-US19048 W 20010614

IT **114899-77-3**, Ecteinascidin 743
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study) (toxicity typing using mesenchymal stem cells)
RN 114899-77-3 HCAPLUS
CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



AB The invention provides methods and systems for identifying and typing toxicity of chemical compns., as well as for screening new compns. for toxicity. The invention involves detecting alterations in gene or protein expression and hence establishing mol. profiles in isolated mammalian MSCs contacted with various chemical compns. of known and unknown toxicities, and correlating the mol. profiles with toxicities of the chemical compns. Application to e.g. screening of anticancer drugs for tissue and organ toxicities is described.
REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 6 OF 76 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:866558 HCAPLUS
DOCUMENT NUMBER: 136:334867
TITLE: The inefficiency of incisions of ecteinascidin 743-DNA adducts by the UvrABC nuclease and the unique structural feature of the DNA adducts can be used to explain the repair-dependent toxicities of this antitumor agent

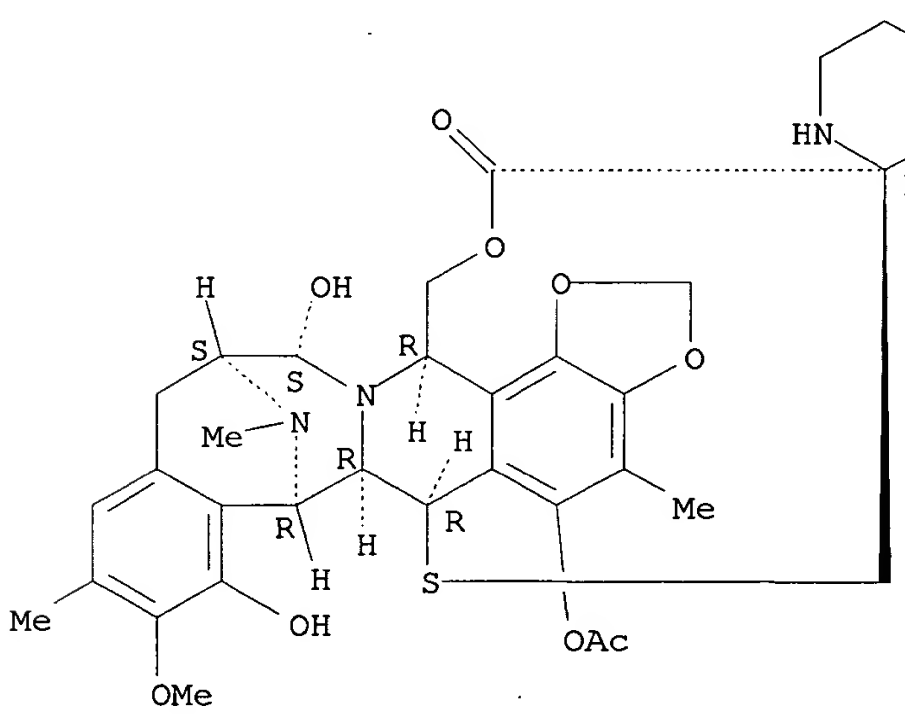
AUTHOR(S): Zewail-Foote, Maha; Li, Ven-Shun; Kohn, Harold; Bearss, David; Guzman, Mary; Hurley, Laurence H.
CORPORATE SOURCE: Department of Chemistry and Biochemistry, The University of Texas at Austin, Austin, TX, 78712, USA
SOURCE: Chemistry & Biology (**2001**), 8(11), 1033-1049
CODEN: CBOLE2; ISSN: 1074-5521
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **114899-77-3**, Ecteinascidin 743
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(mechanism of antitumor ecteinascidin 743 and formation of DNA adducts)

RN 114899-77-3 HCAPLUS

CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



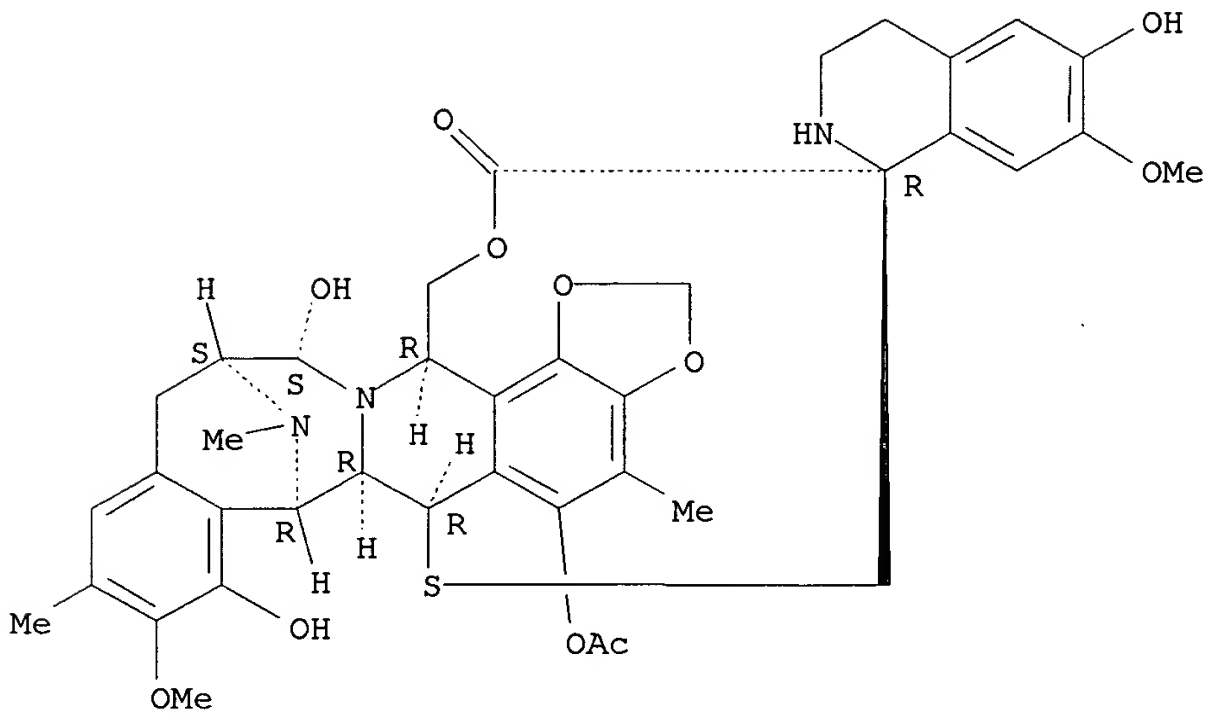
AB Background: Ecteinascidin 743 (Et 743), a natural product derived from a marine tunicate, is a potent antitumor agent presently in phase II clin. trials. Et 743 binds in the minor groove of DNA and alkylates N2 of guanine via a unique mechanism involving catalytic activation. The sequence selectivity of Et 743 is governed by different patterns of hydrogen-bonding to DNA, which results in differential reversibility of the covalent adducts. As determined by NMR spectroscopy, the preferred sequences 5'-PuGC and 5'-PyGG are stabilized by a hydrogen-bonding network, while the non-preferred sequences 5'-NG(A/T) are much less stabilized due to the lack of a key hydrogen bond to the GC base pair on the 3'-side of the alkylated guanine. Results: Mammalian cell lines (XPB, XPD, XPF, XPG, and ERCC1) deficient in the nucleotide excision repair (NER) gene products show resistance to Et 743. The recognition and subsequent incision of Et 743-DNA adducts by the bacterial multisubunit endonuclease UvrABC were used to evaluate DNA repair-mediated toxicity as

a rationale for the resistance of NER-defective cell lines and the antitumor activity of Et 743. The Et 743-DNA adducts are indeed recognized and incised by the UvrABC repair proteins; however, the pattern of incision indicated that the non-preferred, and less stable, sequences (i.e. 5'-NG(A/T)) modified with Et 743 are generally incised at a much higher efficiency than the preferred, more stable sequences (i.e. 5'-PuGC or 5'-PyGG). In addition, within the same Et 743 recognition sequence, the level of incision varies, indicating that flanking regions also contribute to the differential incision frequency. Conclusions: The inefficient repair incision by the UvrABC nuclease of Et 743-DNA adducts provides a basis for rationalizing the observed repair-dependent cytotoxicities of these DNA adducts, if other associated structural properties of Et 743-DNA adducts are taken into account. In particular, the wedge-shaped Et 743, which forces open the minor groove of DNA, introducing a major groove bend, and the extrahelical protrusion of the C-subunit of Et 743 provide unique characteristics alongside the hydrogen-bonding stabilization of a covalent DNA adduct, which we propose traps an intermediate in NER processing of Et 743-DNA adducts. This trapped intermediate protein-Et 743-DNA adduct complex can be considered analogous to a poisoned topoisomerase I- or topoisomerase II-DNA complex. In the absence of an intact NER nuclease complex, this toxic lesion is unable to form, and the Et 743-DNA adducts, although not repaired by the NER pathway, are less toxic to cells. Conversely, elevated levels of either of these nucleases should lead to enhanced Et 743 toxicity.

REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 7 OF 76 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:855438 HCAPLUS
DOCUMENT NUMBER: 137:163219
TITLE: A comparison of limited sampling strategies for prediction of Ecteinascidin 743 clearance when administered as a 24-h infusion
AUTHOR(S): van Kesteren, Charlotte; Mathot, R. A. A.; Lopez-Lazaro, L.; Cvitkovic, E.; Taamma, A.; Jimeno, J. M.; Guzman, C.; Schellens, J. H. M.; Misset, J. L.; Brain, E.; Hillebrand, M. J. X.; Rosing, H.; Beijnen, J. H.
CORPORATE SOURCE: Department of Pharmacy and Pharmacology, The Netherlands Cancer Institute/Slotervaart Hospital, Amsterdam, 1066 EC, Neth.
SOURCE: Cancer Chemotherapy and Pharmacology (**2001**), 48(6), 459-466
CODEN: CCPHDZ; ISSN: 0344-5704
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **114899-77-3**, Ecteinascidin 743
RL: PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(comparison of limited sampling strategies for prediction of Ecteinascidin 743 clearance when administered as a 24-h infusion)
RN 114899-77-3 HCAPLUS
CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



AB Purpose: Ecteinascidin 743 (ET-743) is a novel, marine-derived anticancer agent currently under clin. development for the treatment of solid tumors. The aim of this study was to develop and validate limited sampling strategies for the prediction of ET-743 clearance in phase II studies, using two techniques: the stepwise linear regression approach and the Bayesian estimation approach. Methods: Data from a phase I dose-finding study were used with ET-743 administered as a 24-h infusion. Plasma concentration time
data from 34 patients treated with 1200, 1500 or 1800 μg/m2 ET-743 were randomly divided into an index data set, used for the development of the strategies, and a validation data set. With the linear regression approach, clearance (obtained by non-compartmental anal.) was correlated with the ratios of dose to the observed concns. For the Bayesian approach a three-compartment population pharmacokinetic model was developed; optimal time-points were selected using the D-optimality algorithm. The strategies were compared by assessment of their predictive performance of CL in the validation data set. Results: The linear regression method yielded a single-point sampling schedule with no significant bias and acceptable precision (-0.03% and 21%, resp.). With the Bayesian approach, a three-sample strategy was selected which resulted in less-accurate, but unbiased, predictions (bias 13%, precision 34%). Conclusions: Optimal sampling strategies were developed and validated for estimation of ET-743 clearance. Although the linear regression approach showed slightly better predictive performance, the Bayesian approach is preferred for the current phase II studies as it is more robust and flexible and allows the description of the full pharmacokinetic profile.

REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 8 OF 76 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:837899 HCAPLUS
DOCUMENT NUMBER: 138:348345
TITLE: Antiproliferative activity of ecteinascidin 743 is dependent upon transcription-coupled

nucleotide-excision repair. [Erratum to document cited in CA135:352440]

AUTHOR(S): Takebayashi, Yuji; Pourquier, Philippe; Zimonjic, Drazan B.; Nakayama, Kentaro; Emmert, Steffen; Ueda, Takahiro; Urasaki, Yoshimasa; Kanzaki, Atsuko; Akiyama, Shin-Ichi; Popescu, Nicholas; Kraemer, Kenneth H.; Pommier, Yves

CORPORATE SOURCE: Laboratory of Molecular Pharmacology, Center for Cancer Research, National Cancer Institute, Bethesda, MD, USA

SOURCE: Nature Medicine (New York, NY, United States) (**2001**), 7(11), 1255
CODEN: NAMEFI; ISSN: 1078-8956

PUBLISHER: Nature America Inc.

DOCUMENT TYPE: Journal

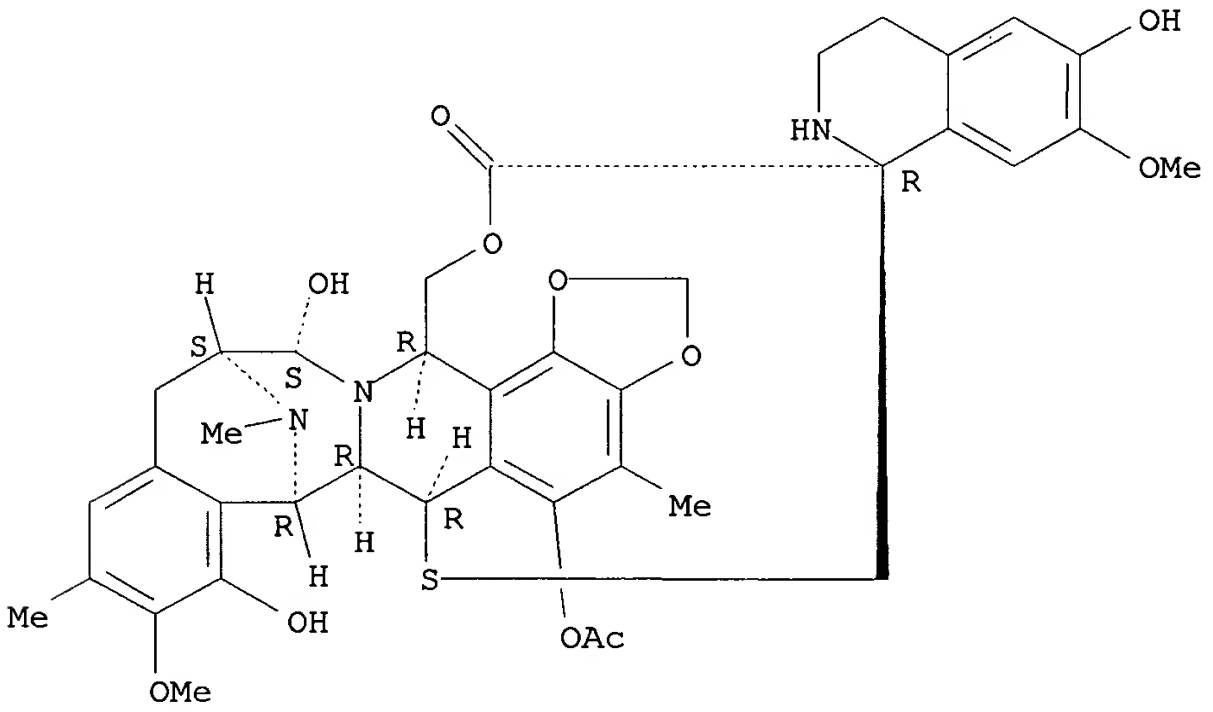
LANGUAGE: English

IT **114899-77-3**, Ecteinascidin 743
RL: BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antiproliferative activity of ecteinascidin 743 is dependent upon transcription-coupled nucleotide-excision repair (Erratum))

RN 114899-77-3 HCAPLUS

CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

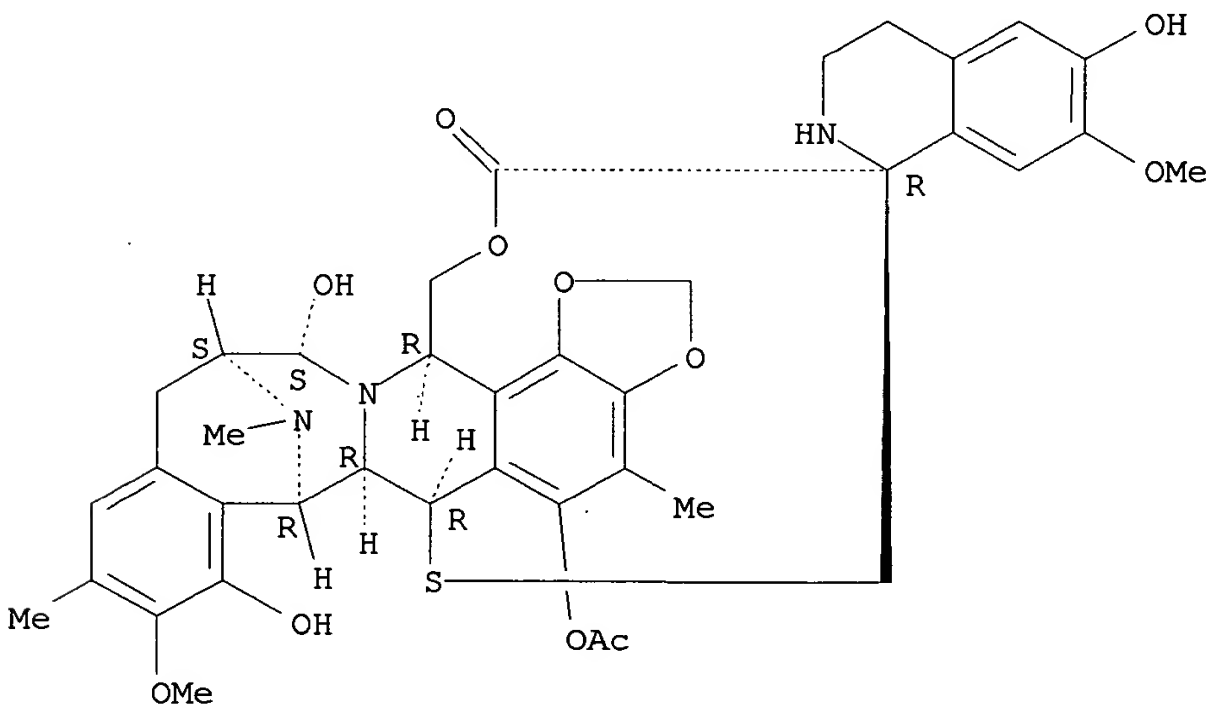


AB On page 962, the symbols in the legend for Figure 2e are incorrect. In the legend, e represents the UV light hypersensitivity of HCT116/ER5 cells analyzed by MTT assay, the solid circle represents HCT116 cells, and the open circle represents HCT116/ER5 cells.

L27 ANSWER 9 OF 76 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:829941 HCAPLUS

DOCUMENT NUMBER: 136:118608
TITLE: Advances in the chemistry and pharmacology of ecteinascidins, a promising new class of anti-cancer agents
AUTHOR(S): Manzanares, I.; Cuevas, C.; Garcia-Nieto, R.; Marco, E.; Gago, F.
CORPORATE SOURCE: Pharma Mar S.A., Tres Cantos, Madrid, E-28760, Spain
SOURCE: Current Medicinal Chemistry: Anti-Cancer Agents (**2001**), 1(3), 257-276
CODEN: CMCACI; ISSN: 1568-0118
PUBLISHER: Bentham Science Publishers Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
IT **114899-77-3P**, ET 743
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(advances in chemical and pharmacol. of ecteinascidins, a promising new class of anti-cancer agents)
RN 114899-77-3 HCAPLUS
CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



AB A review, ecteinascidins are marine natural products consisting of two or three linked tetrahydroisoquinoline subunits and an active carbinolamine functional group. Their potent antiproliferative activity against a variety of tumor cells has made them attractive candidates for development as anticancer agents. The lead compound, ecteinascidin 743 (ET 743), is currently in phase II clin. trials but the low amts. present in its natural source, the tunicate Ecteinascidia turbinata, made it necessary to develop efficient synthetic procedures. Recent improvements on the original synthesis are reviewed as well as new strategies starting from readily available cyanosafracin B. ET 743 is known to bind to the minor

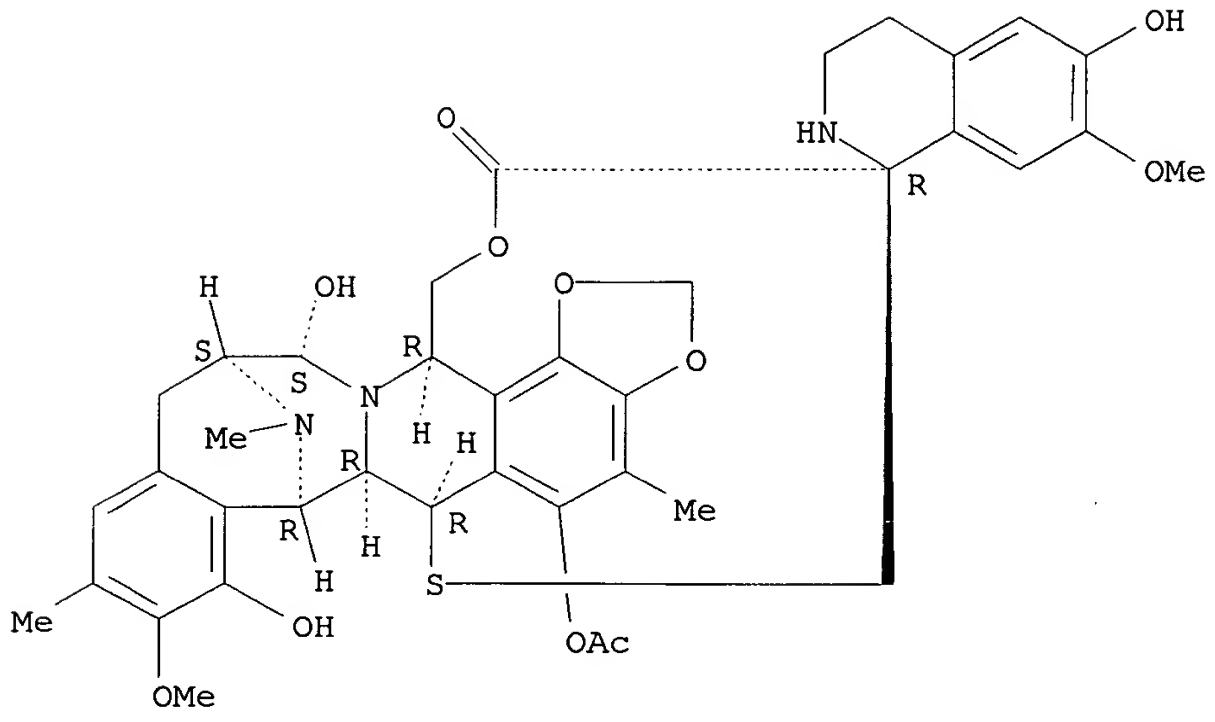
groove of DNA giving rise to a covalent adduct with the exocyclic amino group at position 2 of a guanine in a fashion similar to saframycin antibiotics. Some of the resulting complexes have been studied by a variety of biochem. and spectroscopic methods and also by computer simulations. The rules for sequence specificity have been well established (preferred targets are RGC and YGG, where R and Y stand for purine and pyrimidine, resp.), and it has been shown that binding of ET 743 to DNA is accompanied by minor groove widening and DNA bending towards the major groove. Although the precise target for antitumor action remains to be unambiguously defined, a role in affecting the transcriptional regulation of some inducible genes is rapidly emerging.

REFERENCE COUNT: 82 THERE ARE 82 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 10 OF 76 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:799814 HCAPLUS
DOCUMENT NUMBER: 137:27867
TITLE: Sequence-dependent enhancement of cytotoxicity produced by ecteinascidin 743 (ET-743) with doxorubicin or paclitaxel in soft tissue sarcoma cells
AUTHOR(S): Takahashi, Naoto; Li, Wei Wei; Banerjee, Debabrata; Scotto, Kathleen W.; Bertino, Joseph R.
CORPORATE SOURCE: Program of Molecular Pharmacology and Therapeutics, Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY, 10021, USA
SOURCE: Clinical Cancer Research (**2001**), 7(10), 3251-3257
CODEN: CCREF4; ISSN: 1078-0432
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **114899-77-3**, Ecteinascidin 743
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(enhanced cytotoxicity by ecteinascidin 743 with doxorubicin or paclitaxel in soft tissue sarcoma cells)
RN 114899-77-3 HCAPLUS
CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



AB Ecteinascidin 743 (ET-743) is a potent antitumor agent from the Caribbean tunicate Ecteinascidin turbinata and is presently in clin. trials for human cancers. To better understand how ET-743 might be used clin., the present study used SRB assays to examine the cytotoxicity resulting from combining ET-743 with 3 other antineoplastic agents: doxorubicin (DXR), trimetrexate, and paclitaxel in different administration schedules in 2 soft tissue sarcoma cell lines, HT-1080 and HS-18, in vitro. Concurrent exposure of ET-743 with DXR resulted in synergistic interactions in both cell lines. Addition of ET-743 for 24 h before DXR was the most effective cytotoxic regimen against both cell lines. Morphol. study by fluorescence microscopy revealed that combination treatment of both cells with ET-743 and DXR induced apoptosis. Exposure to paclitaxel before ET-743 was also an effective regimen. These results encourage studies of the combination of ET-743 and DXR in the treatment of soft tissue sarcoma, because each of these agents have activity in this disease.

REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

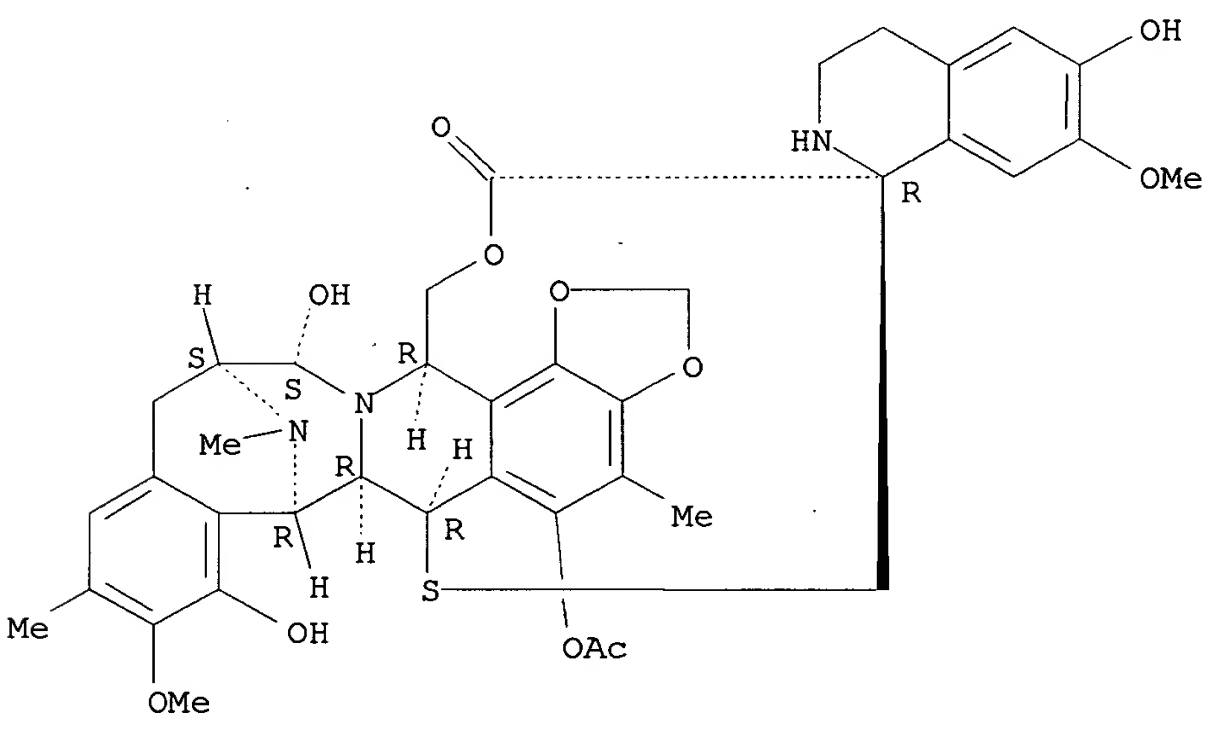
L27 ANSWER 11 OF 76 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:750175 HCAPLUS
DOCUMENT NUMBER: 136:395455
TITLE: Sensitivity of soft tissue sarcoma cell lines to chemotherapeutic agents: identification of ecteinascidin-743 as a potent cytotoxic agent
AUTHOR(S): Li, Wei Wei; Takahashi, Naoto; Jhanwar, Suresh; Cordon-Cardo, Carlos; Elisseyeff, Yaroslav; Jimeno, Jose; Faircloth, Glynn; Bertino, Joseph R.
CORPORATE SOURCE: Laboratories of Molecular Pharmacology, Memorial Sloan-Kettering Cancer Center, New York, NY, 10021, USA
SOURCE: Clinical Cancer Research (**2001**), 7(9), 2908-2911
CODEN: CCREF4; ISSN: 1078-0432
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **114899-77-3,** Ecteinascidin-743
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(sensitivity of soft tissue sarcoma cell lines to chemotherapeutic agents: ecteinascidin-743 as a potent cytotoxic agent)

RN 114899-77-3 HCAPLUS

CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OMe

AB The cytotoxic effects of ecteinascidin-743(ET-743), a novel marine natural product, were evaluated and compared with that of clin. used anticancer agents methotrexate, doxorubicin, etoposide, and paclitaxel in eight human soft tissue sarcoma (STS) cell lines. HT-1080, a fibrosarcoma cell line, and HS-42, a malignant mesodermal cell line, were the most sensitive of the cell lines to methotrexate, doxorubicin, etoposide, and paclitaxel. Other cell lines (IC50s) varied considerably and were more resistant to these agents. ET-743 was more potent than any of these agents, with IC50s in the PM range in all of the cell lines. Cytotoxicity of ET-743 was dose- and time-related (4-72 h exposure). Cytotoxic concns. of ET-743 produced a S/G2 block in all of the cell lines tested. Three colon adenocarcinoma cell lines, HCT-8, HT-29, and HCT-116, and one breast cancer cell line, MCF-7, were 1-2 logs less sensitive to ET-743 than the STS cell lines. Cell lines were also characterized as to expression of oncogenes and tumor suppressor genes to attempt to correlate sensitivity of these cell lines to ET-743 and other chemotherapeutic agents. All of the cell lines except M8805, a malignant fibrous histiocytoma cell line, had mutations in p53 and/or overexpressed the MDM2 protein. Only HS-18, a liposarcoma cell line, lacked expression of the retinoblastoma protein. None of the cell lines had detectable expression of P-glycoprotein as measured by immunohistochem. ET-743 is an extremely potent cytotoxic agent against human STS cell lines and is being evaluated as an antitumor agent in this disease.

REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 12 OF 76 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:730827 HCAPLUS
DOCUMENT NUMBER: 135:267278
TITLE: Methods of modulating drug clearance mechanisms by altering SXR activity
INVENTOR(S): Forman, Barry; Synold, Timothy W.
PATENT ASSIGNEE(S): City of Hope, USA
SOURCE: PCT Int. Appl., 63 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001072837	A2	20011004	WO 2001-US9228	20010323 <--
WO 2001072837	A3	20020523		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

EP 1268547	A2	20030102	EP 2001-926406	20010323

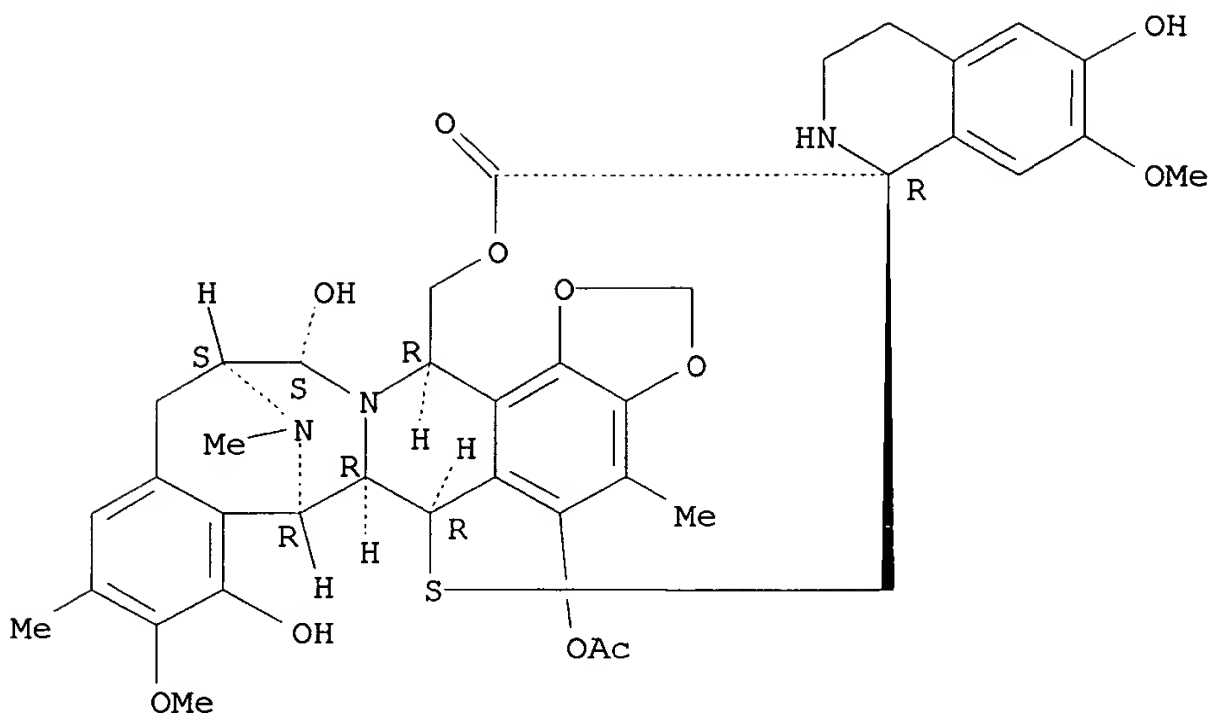
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

JP 2003528889	T2	20030930	JP 2001-571768	20010323

PRIORITY APPLN. INFO.:	US 2000-191767P	P	20000324
	US 2001-266866P	P	20010207
	WO 2001-US9228	W	20010323

IT **114899-77-3**, ecteinascidin-743
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(SXR antagonist; methods of modulating drug pharmacokinetics and metabolism mechanisms by altering SXR activity to modulate MDR1 and cytochrome P 450 3A4 and 2C8 in relation to drug resistance)
RN 114899-77-3 HCAPLUS
CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (9CI) (CA INDEX NAME)

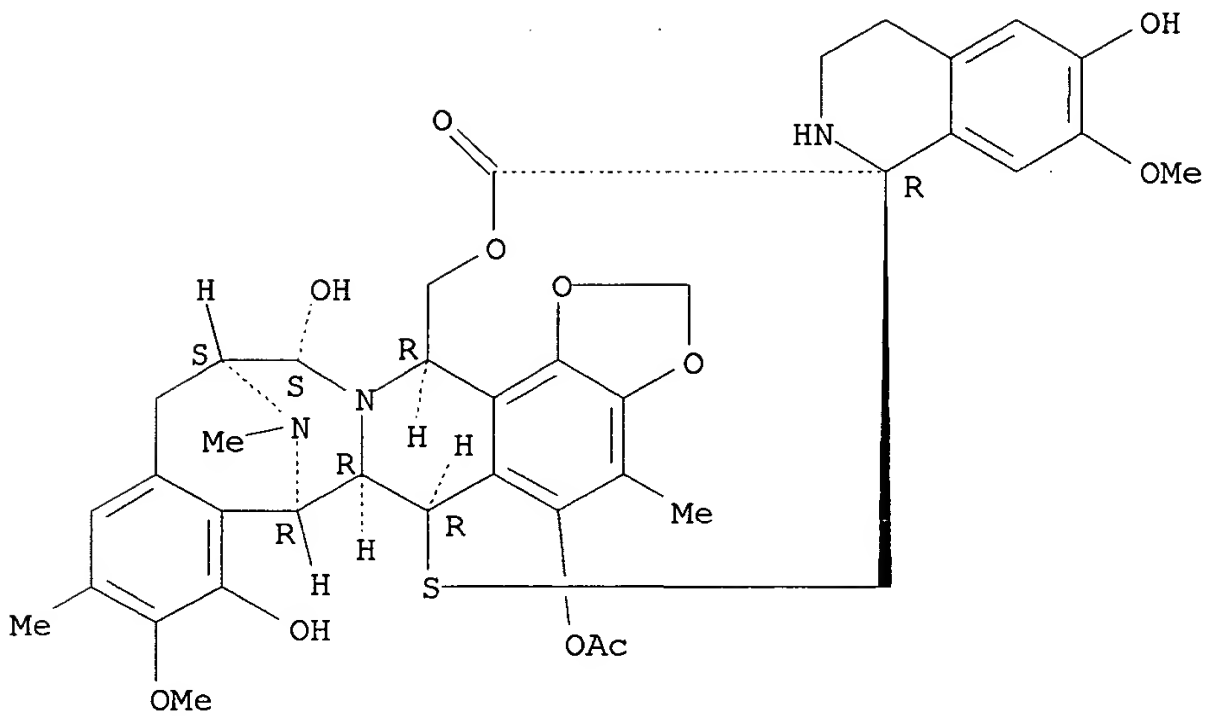
Absolute stereochemistry. Rotation (-).



AB The present invention relates to new methods of modifying drug clearance and avoiding multi-drug resistance by modifying SXR activity. SXR is a transcriptional activator of MDR1, cytochrome P 450-3A4 and cytochrome P 450 2C8. SXR activation can significantly increase the metabolic inactivation and efflux of a wide range of chemotherapeutic agents, for example taxanes. Reducing and/or preventing SXR activation therefore diminishes drug resistance and drug clearance and forms the basis of important therapeutic methods which increase the performance of drugs, such as taxanes. Screening and drug identification methods are described which can identify drugs which are not susceptible to SXR related inactivation and increased efflux. In addition, drugs which can reduce these effects for other agents are provided.

L27 ANSWER 13 OF 76 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:696815 HCAPLUS
DOCUMENT NUMBER: 136:66
TITLE: Sarcoma
AUTHOR(S): Maki, Robert
CORPORATE SOURCE: Memorial Sloan-Kettering Cancer Center, New York, NY, 10021-6007, USA
SOURCE: Oncologist (**2001**), 6(4), 333-337
CODEN: OCOLF6; ISSN: 1083-7159
PUBLISHER: AlphaMed Press
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
IT **114899-77-3**, ET-743
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(systemic therapy for sarcoma in humans)
RN 114899-77-3 HCAPLUS
CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



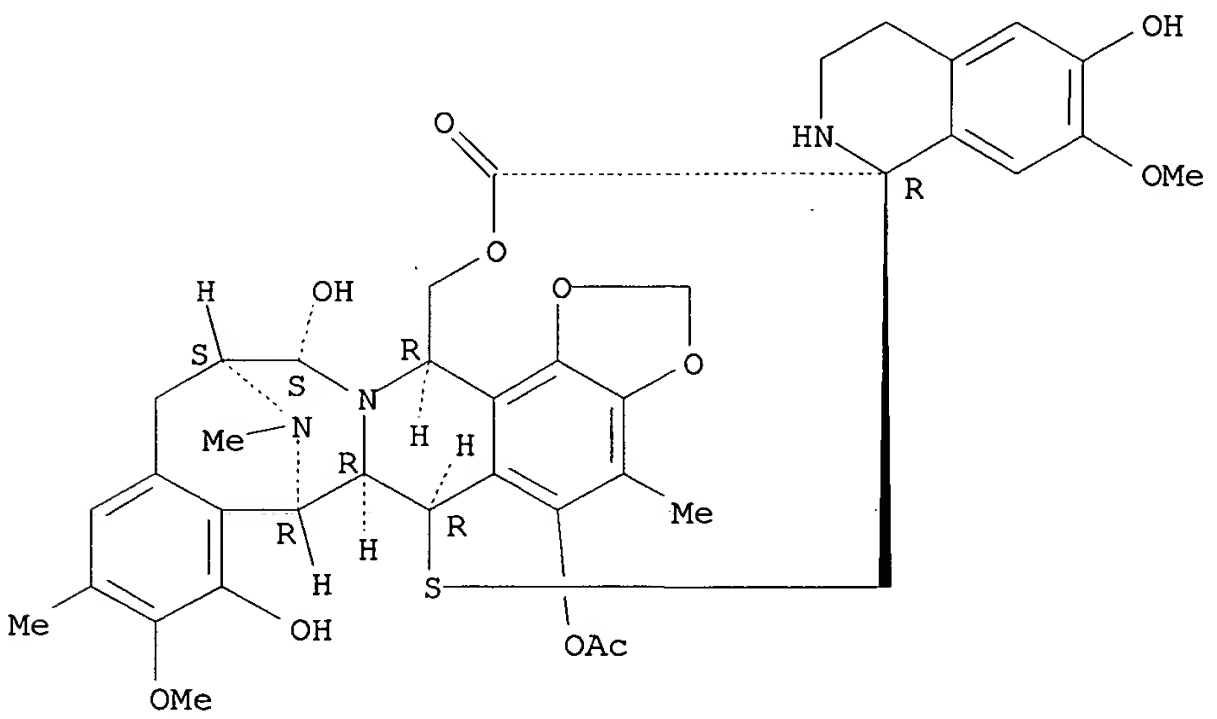
AB A review. ASCO 2001 was a banner year for innovative systemic therapy for sarcomas. Imatinib mesylate (STI571, Gleevec) shows clear activity not only in chronic myelogenous leukemia, for which the drug received Food and Drug Administration approval, but also in gastrointestinal stromal tumors as well, by virtue of imatinib mesylate binding to the abl, kit, and platelet-derived growth-factor receptor tyrosine kinases. Ecteinascidin-743 (ET-743) demonstrates activity against a fraction of other soft-tissue sarcomas. Gemcitabine-based regimens show at least some activity against a subset of soft-tissue sarcomas. Given the lack of new agents for sarcoma therapy since the development of ifosfamide, these studies give hope that the term "effective systemic therapy for sarcoma" might become a reality.

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 14 OF 76 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:688206 HCAPLUS
DOCUMENT NUMBER: 136:79361
TITLE: Evaluation of the use of in vitro methodologies as tools for screening new compounds for potential in vitro toxicity
AUTHOR(S): Luber-Narod, J.; Smith, B.; Grant, W.; Jimeno, J. M.; Lopez-Lazaro, L.; Faircloth, G. T.
CORPORATE SOURCE: PharmaMar USA, Inc., Cambridge, MA, 02139, USA
SOURCE: Toxicology in Vitro (**2001**), 15(4/5), 571-577
CODEN: TIVIEQ; ISSN: 0887-2333
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **114899-77-3**, Ecteinascidin 743
RL: ADV (Adverse effect, including toxicity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(evaluation of use of in vitro methodologies as tools for screening new compds. for potential in vitro toxicity)
RN 114899-77-3 HCAPLUS
CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-

dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



AB The use of in vitro methods as a safety toxicol. screen was evaluated with well-studied standard chemotherapeutic agents. Using the MTS assay (CellTiter 96 aqueous), 5-fluorouracil was found to exhibit myelocytotoxicity only. There was no cytotoxicity to liver, kidney and heart cells, except at very high concns. ET-743 was found to show hepatocytotoxicity, skeletal muscle cytotoxicity, and myelocytotoxicity and, at somewhat higher concns., nephrocytotoxicity and cardiocytotoxicity. A combination of techniques was used to measure neurotoxicity. LDH assay (CytoTox 96) and MTS assay led to comparable results. These techniques determined that ET-743 is selectively cytotoxic to brain glia yet, to some extent, spares neurons. The results obtained agreed well with clin. findings of several known drugs tested.

REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 15 OF 76 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:587819 HCAPLUS
DOCUMENT NUMBER: 135:352440
TITLE: Antiproliferative activity of ecteinascidin 743 is dependent upon transcription-coupled nucleotide-excision repair
AUTHOR(S): Takebayashi, Yuji; Pourquier, Philippe; Zimonjic, Drazen B.; Nakayama, Kentaro; Emmert, Steffen; Ueda, Takahiro; Urasaki, Yoshimasa; Kanzaki, Arsuko; Akiyama, Shin-Ichi; Popescu, Nicholas; Kraemer, Kenneth H.; Pommier, Yves
CORPORATE SOURCE: Laboratory of Molecular Pharmacology, Center for Cancer Research, National Cancer Institute, NIH, Bethesda, MD, USA
SOURCE: Nature Medicine (New York, NY, United States) (

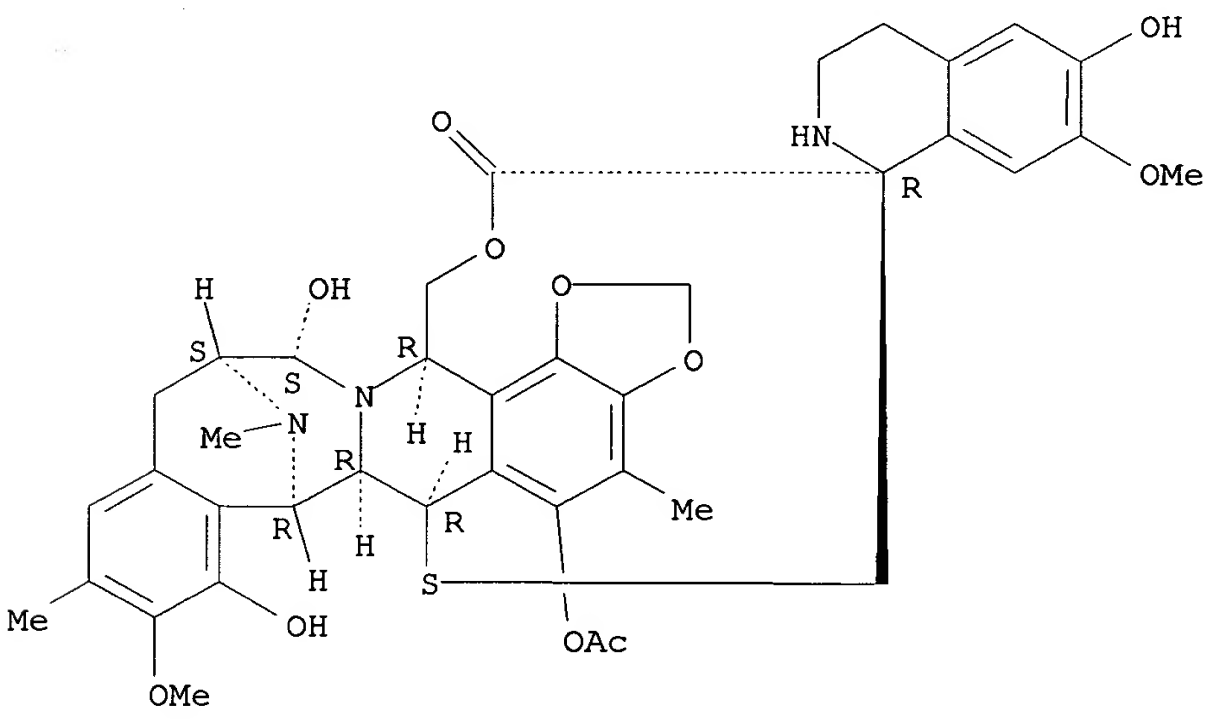
2001), 7(8), 961-966
CODEN: NAMEFI; ISSN: 1078-8956
PUBLISHER: Nature America Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **114899-77-3**, Ecteinascidin 743
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antiproliferative activity of ecteinascidin 743 is dependent upon transcription-coupled nucleotide-excision repair)

RN 114899-77-3 HCAPLUS

CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



AB While investigating the novel anticancer drug ecteinascidin 743 (Et743), a natural marine product isolated from the Caribbean sea squirt, we discovered a new cell-killing mechanism mediated by DNA nucleotide excision repair (NER). A cancer cell line selected for resistance to Et743 had chromosome alterations in a region that included the gene implicated in the hereditary disease xeroderma pigmentosum (XPG, also known as Ercc5). Complementation with wild-type XPG restored the drug sensitivity. Xeroderma pigmentosum cells deficient in the NER genes XPG, XPA, XPD or XPF were resistant to Et743, and sensitivity was restored by complementation with wild-type genes. Moreover, studies of cells deficient in XPC or in the genes implicated in Cockayne syndrome (CSA and CSB) indicated that the drug sensitivity is specifically dependent on the transcription-coupled pathway of NER. We found that Et743 interacts with the transcription-coupled NER machinery to induce lethal DNA strand breaks.

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 16 OF 76 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:545697 HCAPLUS
DOCUMENT NUMBER: 135:137633
TITLE: Preparation of saframycin-ecteinascidin analogs and their therapeutic applications
INVENTOR(S): Danishefsky, Samuel J.; Zhou, Bishan
PATENT ASSIGNEE(S): The Trustees of Columbia University in the City of New York, USA
SOURCE: PCT Int. Appl., 115 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001053299	A1	20010726	WO 2001-US1877	20010119 <--
WO 2001053299	C2	20021024		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2002025962	A1	20020228	US 2001-765515	20010119
EP 1254140	A1	20021106	EP 2001-903151	20010119
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2003520801	T2	20030708	JP 2001-553773	20010119

PRIORITY APPLN. INFO.: US 2000-177071P P 20000119
WO 2001-US1877 W 20010119

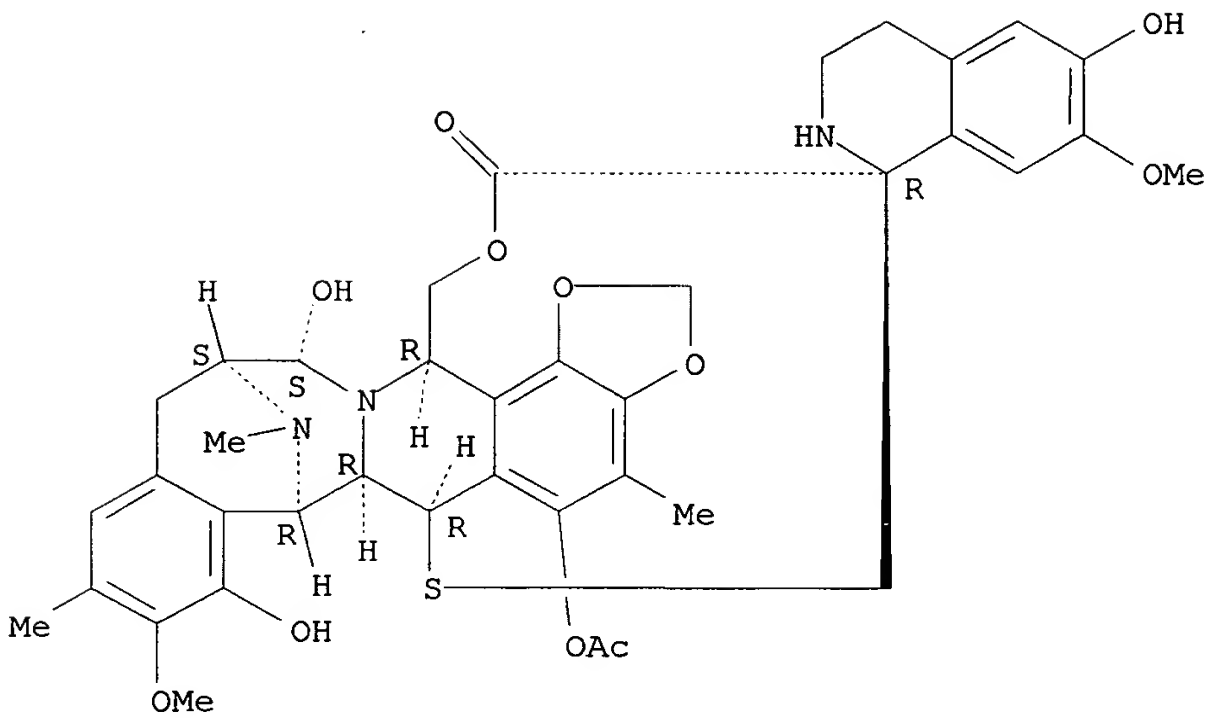
OTHER SOURCE(S): MARPAT 135:137633

IT **114899-77-3P**, ET 743
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PNU (Preparation, unclassified); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(cytotoxicity and antimicrobial activity of)

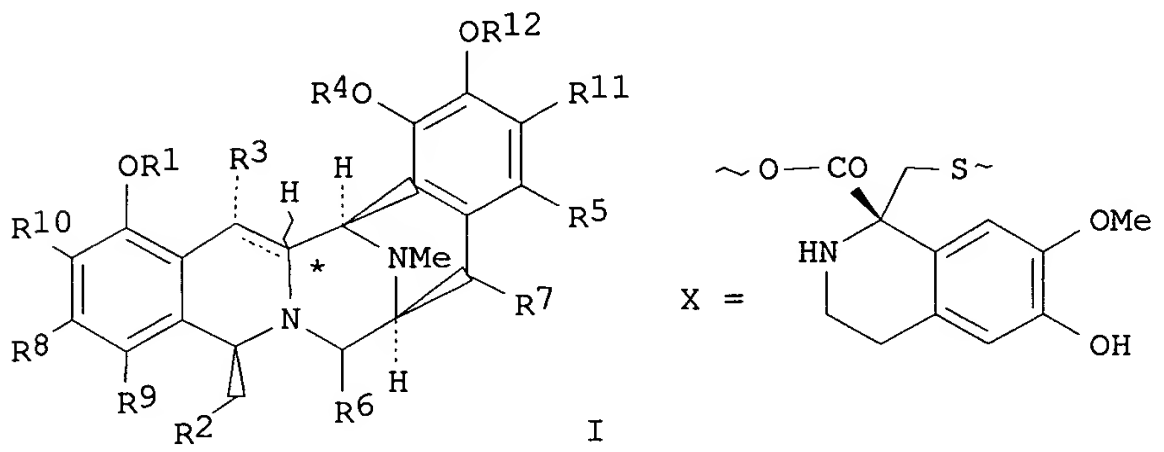
RN 114899-77-3 HCAPLUS

CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (9CI) (CA INDEX NAME)

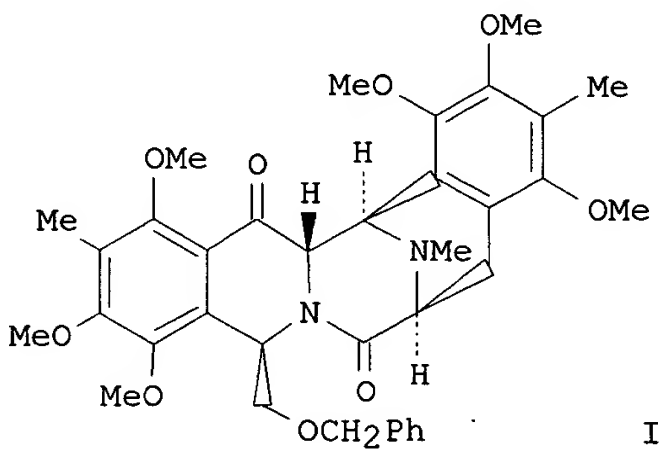
Absolute stereochemistry. Rotation (-).



GI



I



II

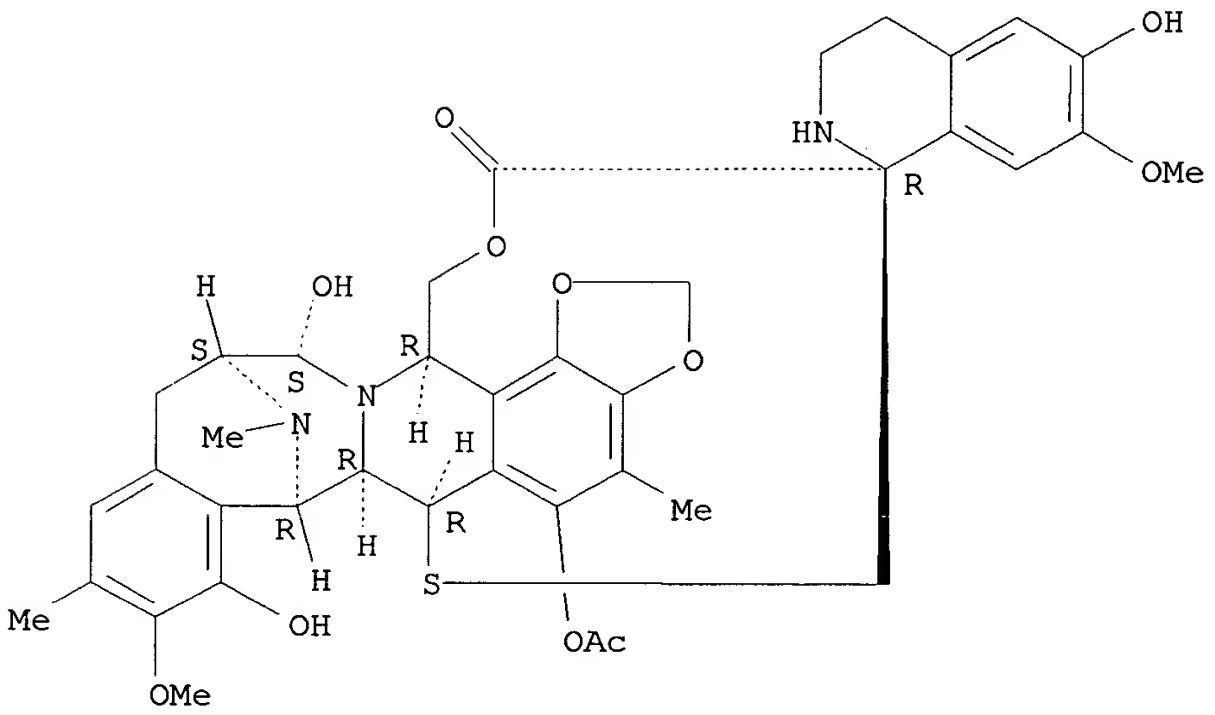
AB Compds. of the saframycin-ecteinascidin series such as I [R1,R4 = H, alkyl, acyl; R3 = =O, OH, ether, sulfide, acyl group such as OC(O)Me, OC(O)Bn and OC(O)Et; R5 = H, halogen, OH, ether, acyl, amide; R6 = =O, OH, OMe, CN, acyloxy; R7 = =O, OH, halogen, ether, acyl; R8 and R9 independently = H, Me, OMe, OEt, CF3, Br, F; R8R9 = OCH2O, five or six

membered ring; R10,R11 = Me, OMe, OEt, SMe, SEt; R12 = H, alkyl, acyl; chiral center marked * has the R or the S configuration], were prepared for use as antitumor and antimicrobial agents. Thus, saframycin analog II was prepared via a multistep synthetic sequence starting from 2,4-Dimethoxy-3-methylbenzaldehyde, bromoacetal, 2-hydroxy-4-methoxy-3-methylbenzaldehyde and [[(2E)-4-bromo-2-butenyl]oxy](1,1-dimethylethyl)dimethylsilane. Ecteinascidin 743 I (R1 = Ac, R2R3 = X, R4 = R5 = R7 = H, R6 = α-OH, R8R9 = OCH2O, R10-R12 = Me) was tested for cytotoxicity and antimicrobial activity.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 17 OF 76 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:440060 HCAPLUS
DOCUMENT NUMBER: 135:174883
TITLE: Differential Rates of Reversibility of Ecteinascidin 743-DNA Covalent Adducts from Different Sequences Lead to Migration to Favored Bonding Sites
AUTHOR(S): Zewail-Foote, Maha; Hurley, Laurence H.
CORPORATE SOURCE: Department of Chemistry and Biochemistry, The University of Texas at Austin, Austin, TX, 78712, USA
SOURCE: Journal of the American Chemical Society (**2001**), 123(27), 6485-6495
CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **114899-77-3**, ecteinascidin 743
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(differential rates of reversibility of ecteinascidin 743-DNA covalent adducts from different sequences lead to migration to favored bonding sites in relation to antitumor activity)
RN 114899-77-3 HCAPLUS
CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



AB Ecteinascidin 743 (Et 743), one of a series of structurally related antitumor antibiotics isolated from a marine tunicate, is currently in phase II clin. trials. Et 743 alkylates guanine N2 through the minor groove of DNA. Hydrogen-bonding networks that associate the drug with a three base pair DNA recognition site have been proposed to contribute to both the reactivity and the stability of the Et 743-DNA adduct. Here, the authors report that the reaction of Et 743 with DNA is reversible under nondenaturing conditions and that the rate of this reverse reaction depends critically upon the DNA-modified sequence. Quite unexpectedly, it was found that although the rates of alkylation are similar for the 5'-AGT and 5'-AGC sequences, reversal from the 5'-AGT sequence occurs faster than from the 5'-AGC sequence. Consequently, it is the differences in the rate of the reverse reaction that dictate the sequence selectivity of Et 743 toward its favored target sequence. As a direct consequence of the reversible nature of Et 743 with DNA, Et 743 can migrate from the nonfavored bonding sequence (e.g., 5'-AGT) to the favored DNA target site (e.g., 5'-AGC). The data suggest that the observed differences in the rate of reversibility arise from differences in the stability of the Et 743-DNA adduct at the 5'-AGT and 5'-AGC target sequences. On the basis of gel electrophoresis and 1H NMR expts., the Et 743-AGT adduct is less stable, has more dynamic motion, and produces different conformational changes in the DNA than the more stable Et 743-AGC adduct. The shuffling of Et 743-DNA adducts to the more stable alkylation sites has important implications for understanding the underlying relation between the structural modification of DNA by Et 743 and its biol. potency and efficacy in tumor cells.

REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 18 OF 76 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:380438 HCAPLUS
DOCUMENT NUMBER: 135:24657
TITLE: Selective cellular targeting: multifunctional delivery vehicles
INVENTOR(S): Glazier, Arnold
PATENT ASSIGNEE(S): Drug Innovation & Design, Inc., USA

SOURCE: PCT Int. Appl., 981 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

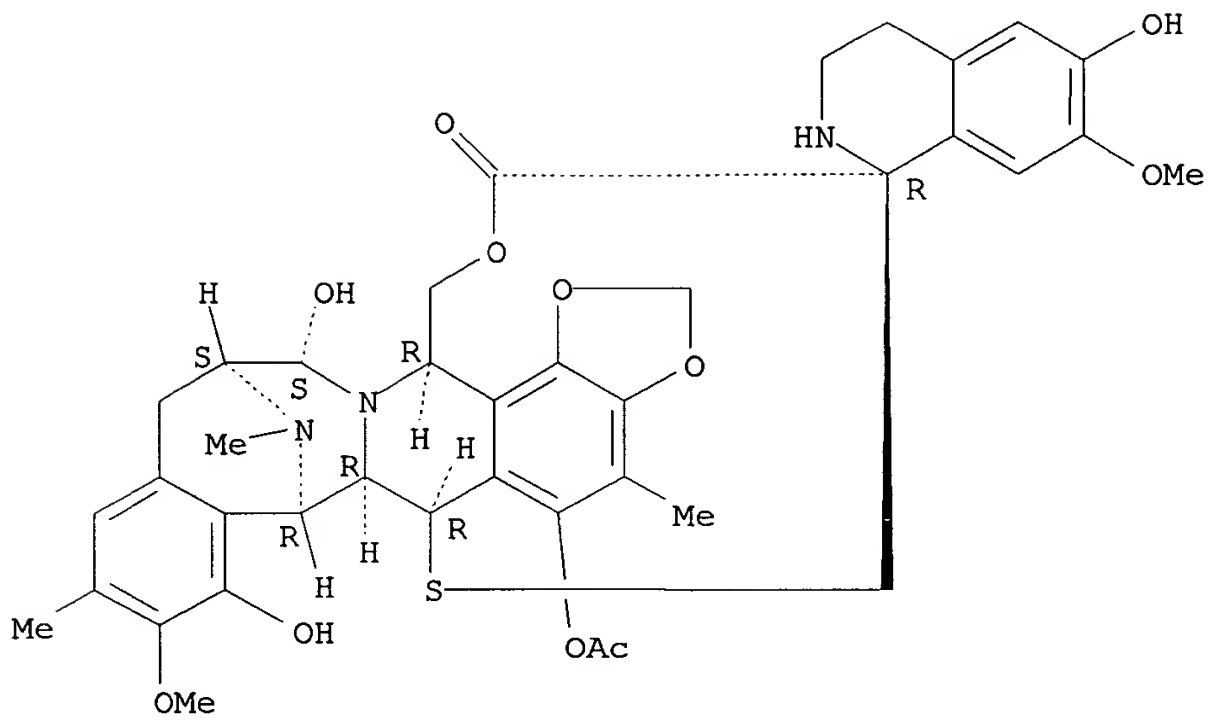
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001036003	A2	20010525	WO 2000-US31262	20001114 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 2001016075	A5	20010530	AU 2001-16075	20001114 <--
EP 1255567	A1	20021113	EP 2000-978631	20001114
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US 2003138432	A1	20030724	US 2000-738625	20001215

PRIORITY APPLN. INFO.:

US 1999-165485P	P	19991115
US 2000-239478P	P	20001011
US 2000-241937P	P	20001020
WO 2000-US31262	W	20001114
US 2000-712465	B1	20001115

IT **114899-77-3D**, Ecteinascidin 743, derivs.
RL: PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(multifunctional delivery vehicles for selective cellular targeting of drugs)
RN 114899-77-3 HCAPLUS
CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

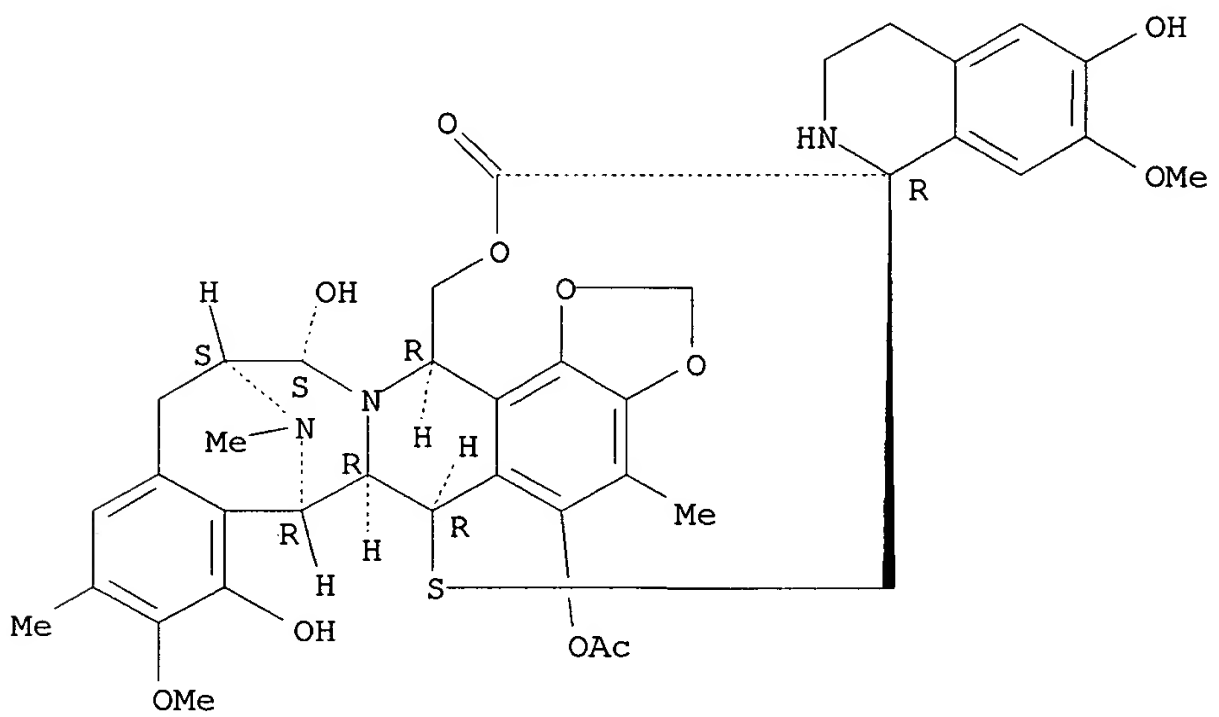


AB The present invention relates to the compns., methods, and applications of a novel approach to selective cellular targeting. The purpose of this invention is to enable the selective delivery and/or selective activation of effector mols. to target cells for diagnostic or therapeutic purposes. The present invention relates to multi-functional prodrugs or targeting vehicles wherein each functionality is capable of enhancing targeting selectivity, affinity, intracellular transport, activation or detoxification. The present invention also relates to ultralow dose, multiple target, multiple drug chemotherapy and targeted immunotherapy for cancer treatment.

L27 ANSWER 19 OF 76 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:363160 HCAPLUS
DOCUMENT NUMBER: 136:130300
TITLE: Unique pattern of ET-743 activity in different cellular systems with defined deficiencies in DNA-repair pathways
AUTHOR(S): Damia, Giovanna; Silvestri, Simonetta; Carrassa, Laura; Filiberti, Laura; Faircloth, Glynn T.; Liberi, Giordano; Foiani, Marco; D'Incalci, Maurizio
CORPORATE SOURCE: Department of Oncology, Instituto di Ricerche Farmacologiche "Mario Negri", Milan, 20157, Italy
SOURCE: International Journal of Cancer (**2001**), 92(4), 583-588
CODEN: IJCNAW; ISSN: 0020-7136
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **114899-77-3**, Ecteinascidin 743
RL: BSU (Biological study, unclassified); DMA (Drug mechanism of action); PAC (Pharmacological activity); BIOL (Biological study)
(ET-743 activity in different cellular systems with defined deficiencies in DNA-repair pathways)
RN 114899-77-3 HCAPLUS
CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one,

5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



AB The cytotoxic activity of ecteinascidin 743 (ET-743), a natural product derived from the marine tunicate Ecteinascidia turbinata that exhibits potent anti-tumor activity in pre-clin. systems and promising activity in phase I and II clin. trials, was investigated in a number of cell systems with well-defined deficiencies in DNA-repair mechanisms. ET-743 binds to N2 of guanine in the minor groove, but its activity does not appear to be related to DNA-topoisomerase I poisoning as the drug is equally active in wild-type yeast and in yeast with a deletion in the DNA-topoisomerase I gene. Defects in the mismatch repair pathway, usually associated with increased resistance to methylating agents and cisplatin, did not affect the cytotoxic activity of ET-743. However, ET-743 did show decreased activity (from 2- to 8-fold) in nucleotide excision repair (NER)-deficient cell lines compared to NER-proficient cell lines, from either hamsters or humans. Restoration of NER function sensitized cells to ET-743 treatment. The DNA double-strand-break repair pathway was also investigated using human glioblastoma cell lines MO59K and MO59J, resp., proficient and deficient in DNA-dependent protein kinase (DNA-PK), ET-743 was more effective in cells lacking DNA-PK; moreover, pre-treatment of HCT-116 colon carcinoma cells with wortmannin, a potent inhibitor of DNA-PK, sensitized cells to ET-743. An increase in ET-743 sensitivity was also observed in ataxia telangiectasia-mutated cells. The data strongly suggest that ET-743 has a unique mechanism of interaction with DNA.

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 20 OF 76 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:342790 HCAPLUS
DOCUMENT NUMBER: 135:131706
TITLE: The orphan nuclear receptor SXR coordinately regulates drug metabolism and efflux
AUTHOR(S): Synold, Timothy W.; Dussault, Isabelle; Forman, Barry

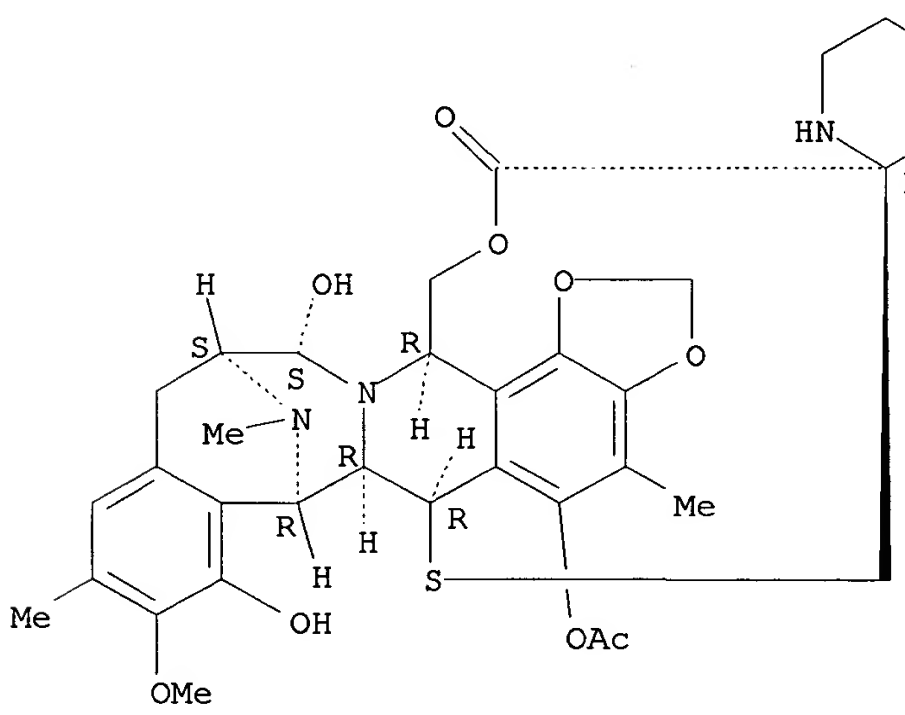
Marc
CORPORATE SOURCE: Department of Medical Oncology and Therapeutics Research, The Beckman Research Institute, City of Hope National Medical Center, Duarte, CA, USA
SOURCE: Nature Medicine (New York, NY, United States) (**2001**), 7(5), 584-590
CODEN: NAMEFI; ISSN: 1078-8956
PUBLISHER: Nature America Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **114899-77-3**, ecteinascidin-743
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(orphan nuclear receptor SXR coordinately regulates drug metabolism and efflux)

RN 114899-77-3 HCAPLUS

CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



AB Cytochrome P 450 3A4 is an important mediator of drug catabolism that can be regulated by the steroid and xenobiotic receptor (SXR). We show here that SXR also regulates drug efflux by activating expression of the gene MDR1, which encodes the protein P-glycoprotein (ABCB1). Paclitaxel (Taxol), a commonly used chemotherapeutic agent, activated SXR and enhanced P-glycoprotein-mediated drug clearance. In contrast, docetaxel (Taxotere), a closely related antineoplastic agent, did not activate SXR and displayed superior pharmacokinetic properties. Docetaxel silent properties reflect its inability to displace transcriptional corepressors from SXR. We also found that ET-743, a potent antineoplastic agent, suppressed MDR1 transcription by acting as an inhibitor of SXR. These findings demonstrate how the mol. activities of SXR can be manipulated to

control drug clearance.
REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

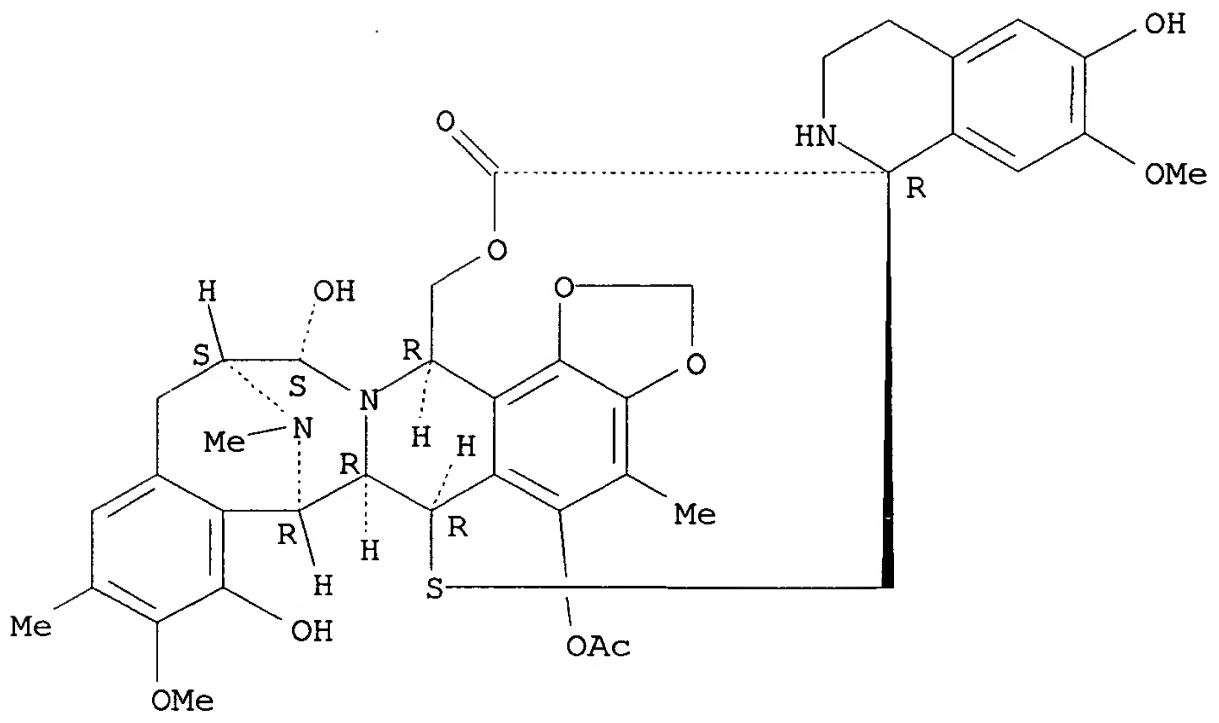
L27 ANSWER 21 OF 76 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:283821 HCAPLUS
DOCUMENT NUMBER: 134:316086
TITLE: Manufacture of polyglutamate-therapeutic agent conjugates
INVENTOR(S): Kumar, Anil M.; Klein, J. Peter; Bhatt, Rama; Vawter, Edward
PATENT ASSIGNEE(S): Cell Therapeutics, Inc., USA
SOURCE: PCT Int. Appl., 44 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001026693	A2	20010419	WO 2000-US28109	20001012 <--
WO 2001026693	A3	20011227		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1225917	A2	20020731	EP 2000-972079	20001012
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
JP 2003511423	T2	20030325	JP 2001-529754	20001012
BR 2000014652	A	20030610	BR 2000-14652	20001012
NO 2002001701	A	20020523	NO 2002-1701	20020411

PRIORITY APPLN. INFO.: US 1999-159135P P 19991012
WO 2000-US28109 W 20001012

IT **114899-77-3DP**, Ecteinascidin 743, conjugates
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(manufacture of polyglutamate-therapeutic agent conjugates)
RN 114899-77-3 HCAPLUS
CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

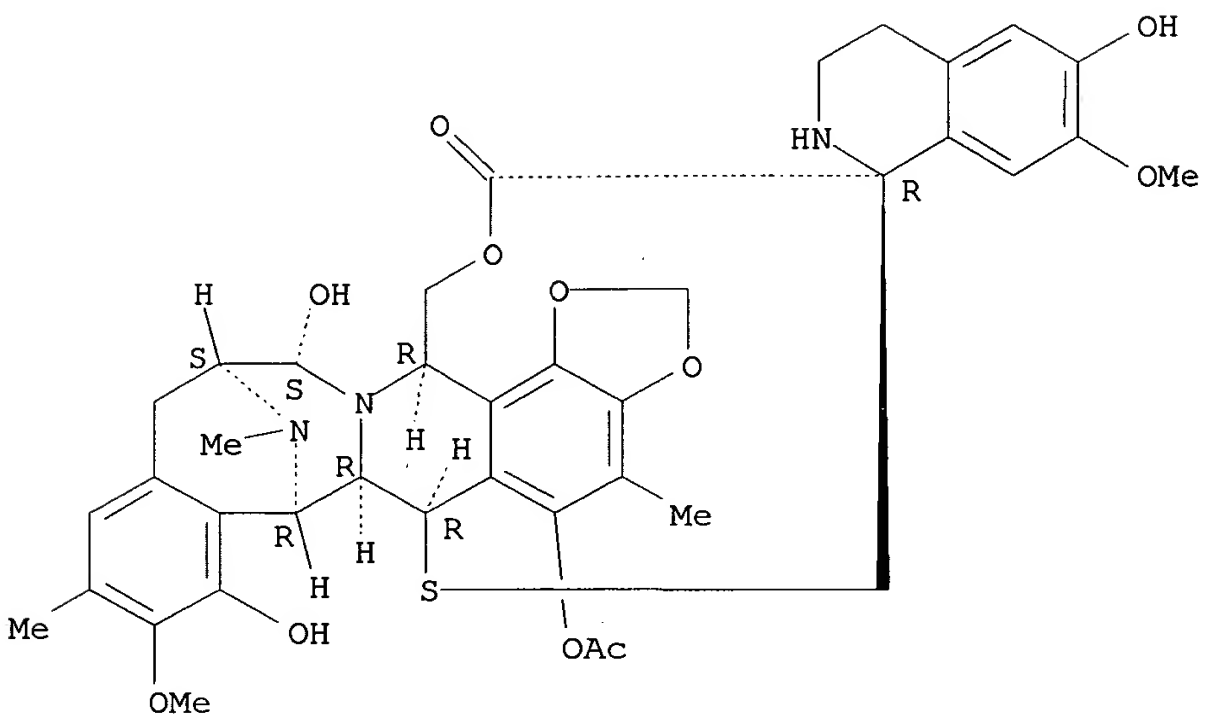


AB The invention provides new processes for preparing polyglutamic acid-therapeutic agent conjugates for clin. development and pharmaceutical use, and polyglutamic acid-therapeutic agent conjugates prepared by these processes. Poly(L-glutamic acid) in N,N-dimethylformamide was reacted with paclitaxel in presence of N,N-diisopropylcarbodiimide to obtain poly-L-glutamic acid-2'-paclitaxel conjugate.

L27 ANSWER 22 OF 76 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:223848 HCAPLUS
DOCUMENT NUMBER: 135:189878
TITLE: Phase I and pharmacokinetic study of ecteinascidin-743, a new marine compound, administered as a 24-hour continuous infusion in patients with solid tumors
AUTHOR(S): Taamma, A.; Misset, J. L.; Riofrio, M.; Guzman, C.; Brain, E.; Lazaro, L. Lopez; Rosing, H.; Jimeno, J. M.; Cvitkovic, E.
CORPORATE SOURCE: Hopital Paul Brousse, Villejuif, 94800, Fr.
SOURCE: Journal of Clinical Oncology (**2001**), 19(5), 1256-1265
CODEN: JCONDN; ISSN: 0732-183X
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **114899-77-3**, ecteinascidin 743
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(phase I and pharmacokinetic study of ecteinascidin-743, a new marine compound, administered as a 24-h continuous infusion in patients with solid tumors)
RN 114899-77-3 HCAPLUS
CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (9CI) (CA

INDEX NAME)

Absolute stereochemistry. Rotation (-).



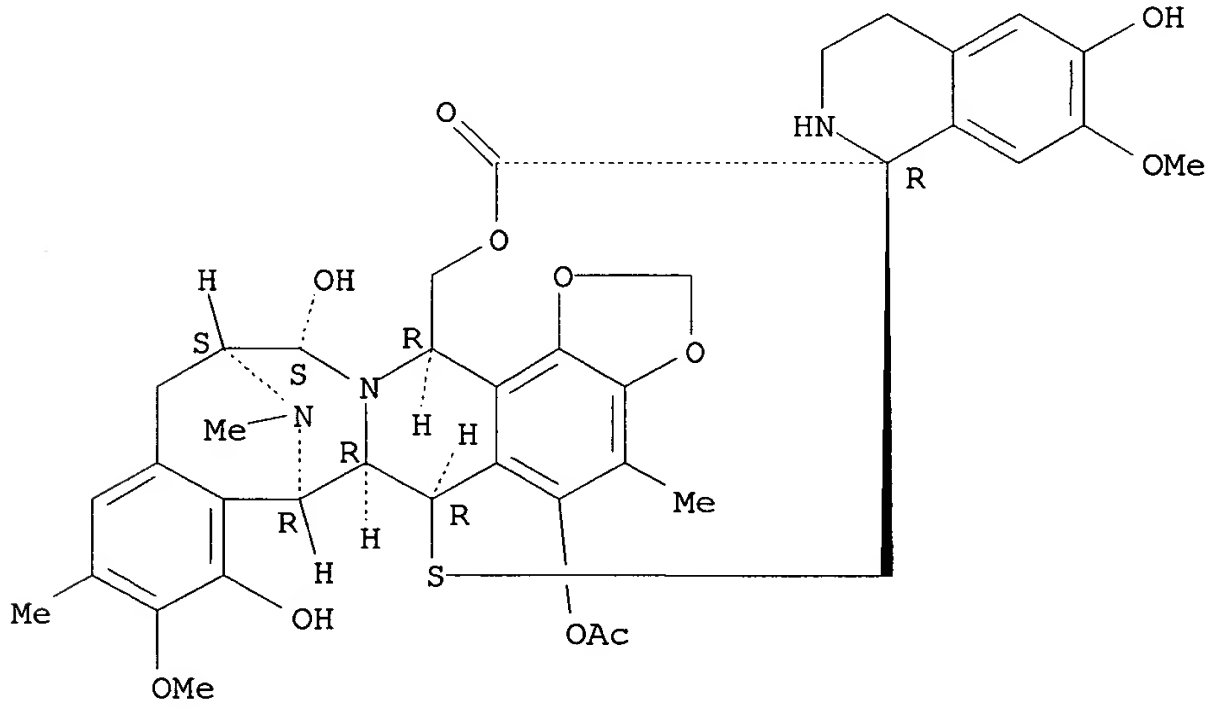
AB Purpose: To define the maximum-tolerated dose (MTD) and the phase II recommended dose (RD) of ecteinascidin-743 (ET-743) given as a 24-h continuous infusion every 3 wk to patients with treatment-refractory solid tumors. Patients and Methods: Fifty-two patients received a total of 158 cycles of ET-743 at one of nine dose levels (DLs) ranging from 50 to 1,800 μg/m2. Results: The MTD was defined as 1,800 μg/m2 (DL 9), and the phase II RD was 1,500 μg/m2 (DL 8) for moderately pretreated patients with performance status (PS) 0 to 1 and good hepatobiliary function. Neutropenia and thrombocytopenia were the dose-limiting toxicities (DLTs) and were severe at the MTD (1,800 μg/m2) in 94% and 25% of cycles, resp. At the RD (1,500 μg/m2), neutropenia and thrombocytopenia were present in 33% and 10% of cycles, resp. Transient acute elevated transaminase levels occurred in almost all cycles and was severe in 38% of cycles. Severe toxicities and DLTs were observed in patients with poor PS or abnormal liver function or who had received a large number of previous chemotherapy regimens. Antitumor activity was observed at the three highest DLs, including three partial responses (breast cancer, osteosarcoma, and liposarcoma), and four patients (all with progressing soft tissue sarcomas) had stable disease lasting ≥ 3 mo. Pharmacokinetic studies were performed on all patients for at least the first cycle, giving a linear pharmacokinetic profile; this showed a relationship between area under the curve (AUC) and transaminitis grade and a clear correlation between AUC and severe hematol. toxicity likelihood. Conclusion: The RD for a 24-h continuous i.v. infusion of ET-743 is 1,500 μg/m2, with the most prevalent DLTs being hematol. Patients with minor baseline hepatobiliary function abnormalities have a higher likelihood of severe hematol. toxicities and AUC-related DLTs, requiring dose adjustments or delays.

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 23 OF 76 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:223847 HCAPLUS

DOCUMENT NUMBER: 135:189877
TITLE: Ecteinascidin-743: a marine-derived compound in advanced, pretreated sarcoma patients-preliminary evidence of activity
AUTHOR(S): Delaloge, S.; Yovine, A.; Taamma, A.; Riofrio, M.; Brain, E.; Raymond, E.; Cottu, P.; Goldwasser, F.; Jimeno, J.; Misset, J. L.; Marty, M.; Cvitkovic, E.
CORPORATE SOURCE: Hopital Paul Brousse and Institut Gustave Roussy, Villejuif, 94800, Fr.
SOURCE: Journal of Clinical Oncology (**2001**), 19(5), 1248-1255
CODEN: JCONDN; ISSN: 0732-183X
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **114899-77-3**, ecteinascidin 743
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ecteinascidin-743, a marine-derived compound in advanced, pretreated sarcoma patients)
RN 114899-77-3 HCAPLUS
CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



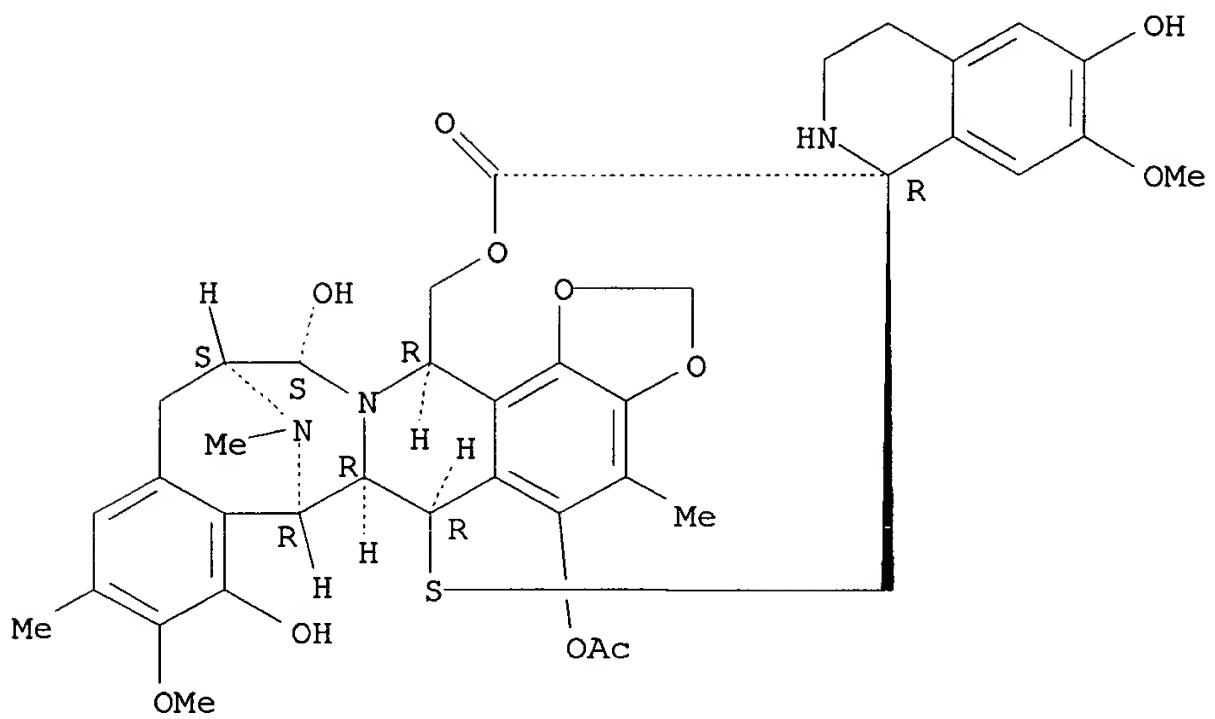
AB Purpose: To report the activity of the chemotherapeutic agent ecteinascidin-743 (ET-743) in advanced pretreated sarcoma patients observed during a phase I study and a named-patient basis, compassionate use program. Patients and Methods: Twenty-nine pretreated, advanced soft tissue sarcoma (STS) and bone sarcoma patients consecutively seen in our centers were included, 12 from a phase I trial and 17 from a compassionate use program cohort. Patients were treated every 3 wk at either 1,200

μg/m2 (six patients), 1,500 μg/m2 (the recommended dose, 22 patients), or 1,800 μg/m2 (the maximum-tolerated dose, one patient), given as a 24-h infusion every 3 to 4 wk. Results: Fifteen men and 14 women were treated. The median patient age was 46 yr (range, 16 to 71 yr), with a median World Health Organization performance status of 1 (range, 0 to 2). Twenty-five patients had STS, three had osteosarcoma, and one had Ewing's sarcoma, and all had progressive disease at accrual. Fifteen patients had bulky disease, and 14 had clin. resistance to anthracyclines. A total of 136 treatment cycles were administered (median per patient, five cycles; range, one to 12 cycles). Transient grade 3 and 4 transaminitis was reported in 24% and 5% of cycles, resp., grade 3 to 4 neutropenia occurred in 32% of cycles, with concomitant sporadic grade 3 to 4 thrombocytopenia in 5.1% of cycles. Grade 2 to 3 asthenia occurred in 21% of cycles. There were two partial responses (PRs) in STS patients and two PRs in osteosarcoma patients. Two minor responses and 10 disease stabilizations were seen. Median duration of response was 10.5 mo (range, 2.8 to 15 mo), and mean duration of stabilization was 5.2 mo. Conclusion: ET-743 has activity in advanced, highly pretreated STS and osteosarcoma patients and warrants further trials to establish the extent of its activity in this setting.

REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 24 OF 76 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:196418 HCAPLUS
DOCUMENT NUMBER: 135:174813
TITLE: Phase I and pharmacokinetic study of ecteinascidin 743 administered as a 72-hour continuous intravenous infusion in patients with solid malignancies
AUTHOR(S): Ryan, David P.; Supko, Jeffrey G.; Eder, J. Paul; Seiden, Michael V.; Demetri, George; Lynch, Thomas J.; Fischman, Alan J.; Davis, John; Jimeno, Jose; Clark, Jeffrey W.
CORPORATE SOURCE: Massachusetts General Hospital, Boston, MA, 02115, USA
SOURCE: Clinical Cancer Research (**2001**), 7(2), 231-242
CODEN: CCREF4; ISSN: 1078-0432
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **114899-77-3**, Ecteinascidin 743
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(ecteinascidin 743 dose limiting toxicity and pharmacokinetics in humans with solid malignancies)
RN 114899-77-3 HCAPLUS
CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



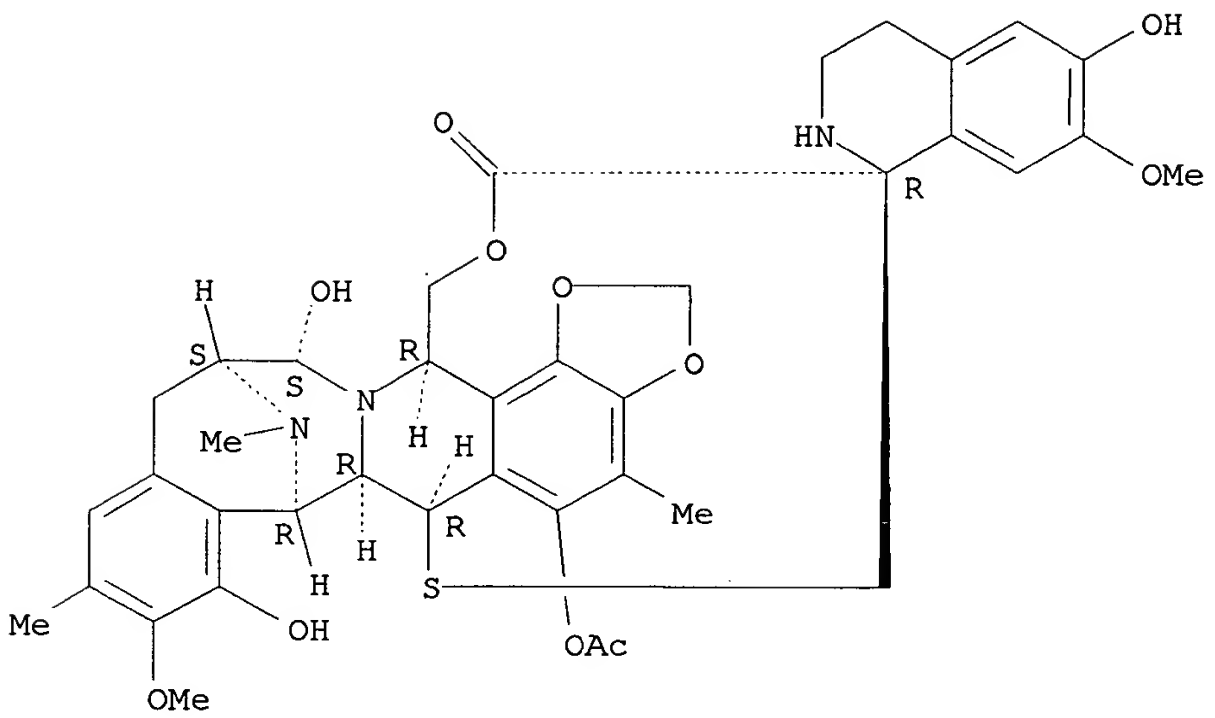
AB Ecteinascidin 743 (ET-743) is a cytotoxic tetrahydroiso-quinoline alkaloid that covalently binds to DNA in the minor groove. The in vitro chemosensitivity of cancer cells to ET-743 is markedly enhanced by prolonging the duration of exposure to the drug. A Phase I study of ET-743 given as a 72-h continuous i.v. infusion every 21 days was performed. Characteristics of the 21 adult patients with refractory solid tumors enrolled in the study were as follows: (a) 12 men; (b) 9 women; (c) median age, 59 yr; (d) Eastern Cooperative Oncol. Group performance status ≤1, 20 patients; and (e) two prior regimens of chemotherapy, 7 patients. Dose limiting toxicity (DLT) was defined by typical criteria, except that grade 3 transaminitis did not constitute a DLT. There were no DLTs in the six patients evaluated at the first two dose levels of 600 and 900 μg/m2. Reversible grade 4 transaminitis occurred in two of nine patients after treatment with the first cycle of therapy at the third dose level of 1200 μg/m2. Another patient experienced grade 4 rhabdomyolysis, renal failure requiring hemodialysis, grade 4 neutropenia, and grade 3 thrombocytopenia during the second cycle of therapy with this dose. The maximum tolerated dose was 1200 μg/m2, and an addnl. six patients were enrolled at an intermediate dose level of 1050 μg/m2. This well-tolerated dose was established as the recommended Phase II dose. The disposition of ET-743 was distinctly biexponential, and a departure from linear pharmacokinetic behavior was evident at the 1200-μg/m2 dose level. Pharmacokinetic parameters determined at 1050 μg/m2 were (mean ± SD): maximum plasma concentration, 318 ± 147 pg/mL; initial disposition phase half-life, 9.0 ± 10.3 min; terminal phase half-life, 69.0 ± 56.7 h; and total plasma clearance, 28.4 ± 22.5 L/h/m2. Prolonged systemic exposure to concns. of the agent that are cytotoxic in vitro were achieved. Toxicity of the drug is clearly schedule-dependent, because increasing the duration of infusion from 3 or 24 h to 72 h results in decreased myelosuppression and comparable hepatotoxicity. Although there were no objective responses to therapy, clear evidence of antitumor activity was observed in a patient with epithelioid mesothelioma, as confirmed by positron emission tomog. studies. A Phase II trial to assess the efficacy of ET-743 against this highly refractory neoplasm has been initiated on the basis of this observation. The therapeutically optimal administration schedule remains to be established, in as much as there

have been indications of activity against a variety of tumors during Phase I studies when the drug was infused over times ranging from 1 to 72 h. Characterizing the pharmacokinetics of ET-743 during the course of Phase II trials and Phase I combination studies is recommended to assure that this promising new anticancer drug can be used with an acceptable margin of safety.

REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 25 OF 76 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:121251 HCAPLUS
DOCUMENT NUMBER: 135:131923
TITLE: Ecteinascidin 743 induces protein-linked DNA breaks in human colon carcinoma HCT116 cells and is cytotoxic independently of topoisomerase I expression
AUTHOR(S): Takebayashi, Yuji; Goldwasser, Francois; Urasaki, Yoshimasa; Kohlhagen, Glenda; Pommier, Yves
CORPORATE SOURCE: Laboratory of Molecular Pharmacology, Division of Basic Sciences, National Cancer Institute, NIH, Bethesda, MD, 20892-4255, USA
SOURCE: Clinical Cancer Research (**2001**), 7(1), 185-191
CODEN: CCREF4; ISSN: 1078-0432
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **114899-77-3**, Ecteinascidin 743
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ecteinascidin 743 induces protein-linked DNA breaks in human colon carcinoma HCT116 cells and is cytotoxic independently of topoisomerase I expression)
RN 114899-77-3 HCAPLUS
CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



AB Ecteinascidin 743 (Et743; NSC 648766) is a potent antitumor agent presently in clin. trials. Et743 selectively alkylates guanine N2 from the minor groove of duplex DNA and bends the DNA toward the major groove. This differentiates Et743 from other DNA-alkylating agents presently in the clinic. To date, the cellular effects of Et743 have not been elucidated. Recently, Et743 DNA adducts have been found to suppress gene expression selectively and to induce topoisomerase I (top1) cleavage complexes in vitro and top1-DNA complexes in cell culture. In the present study, the authors characterized the DNA damage and the cell cycle response induced by Et743 in human colon carcinoma HCT116 cells. Alkaline elution expts. demonstrated that micromolar concns. of Et743 produced comparable frequencies of DNA-protein crosslinks and DNA single-strand breaks. The single-strand breaks were protein-crosslinked and were not associated with detectable DNA double-strand breaks. By contrast with camptothecin, these lesions persisted for several hours after drug removal and were not formed at 4°C. Et743 treatment induced transient p53 elevation, dose-dependent cell cycle accumulation in G2-M and in G1- and S-phase, and inhibition of DNA synthesis. The sensitivity of camptothecin-resistant mouse leukemia P388/CPT45 cells, which fail to express detectable top1, was similar to the sensitivity of wild-type P388 cells, suggesting that top1 is not a critical target for the antiproliferative activity of Et743.

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 26 OF 76 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:85100 HCAPLUS
DOCUMENT NUMBER: 134:281010
TITLE: Sequential Staudinger/Pictet-Spengler cyclization strategy for the construction of tetrahydroisoquinolines of the bioxalomycin and ecteinascidin family of alkaloids
AUTHOR(S): Herberich, B.; Kinugawa, M.; Vazquez, A.; Williams, R. M.
CORPORATE SOURCE: Department of Chemistry, Colorado State University, Fort Collins, CO, 80523, USA

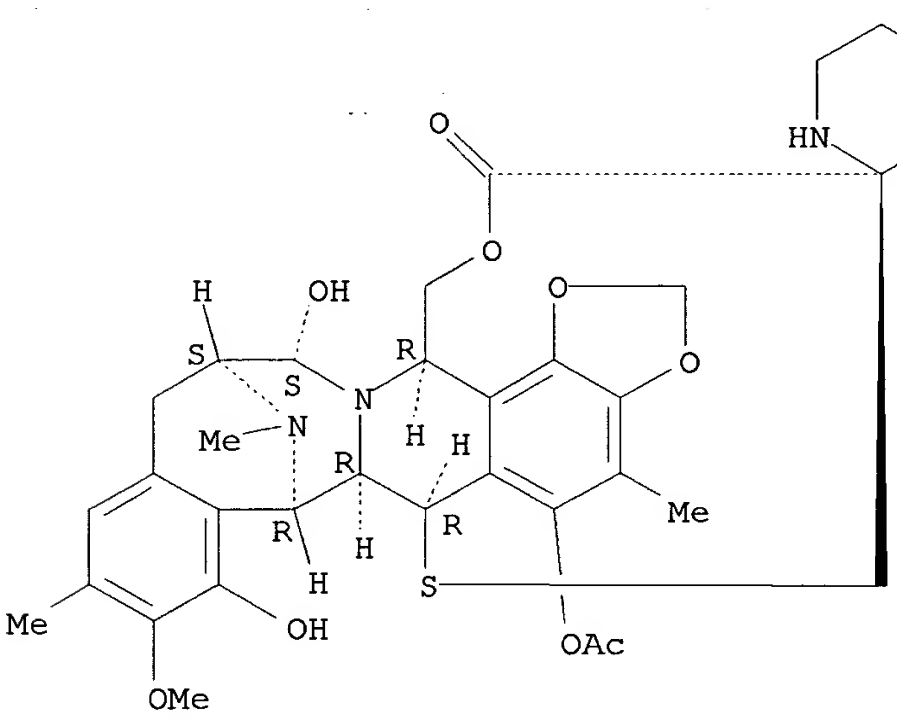
SOURCE: Tetrahedron Letters (**2001**), 42(4), 543-546
CODEN: TELEAY; ISSN: 0040-4039
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 134:281010

IT **114899-77-3P**, Ecteinascidin 743
RL: PNU (Preparation, unclassified); PREP (Preparation)
(sequential Staudinger/Pictet-Spengler cyclization strategy for preparation of the tetrahydroisoquinoline core of bioxalomycin and ecteinascidin alkaloids)

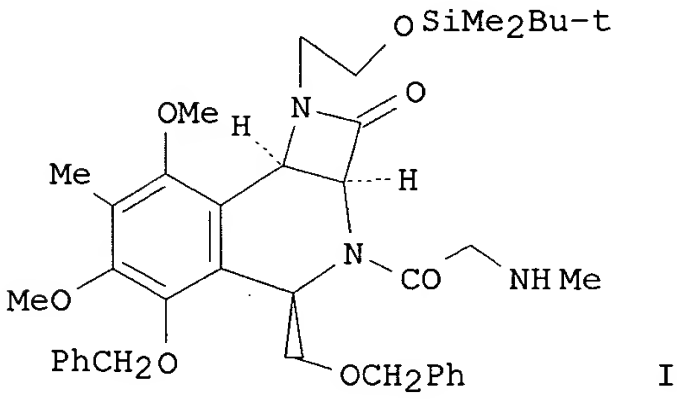
RN 114899-77-3 HCAPLUS

CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



GI



I

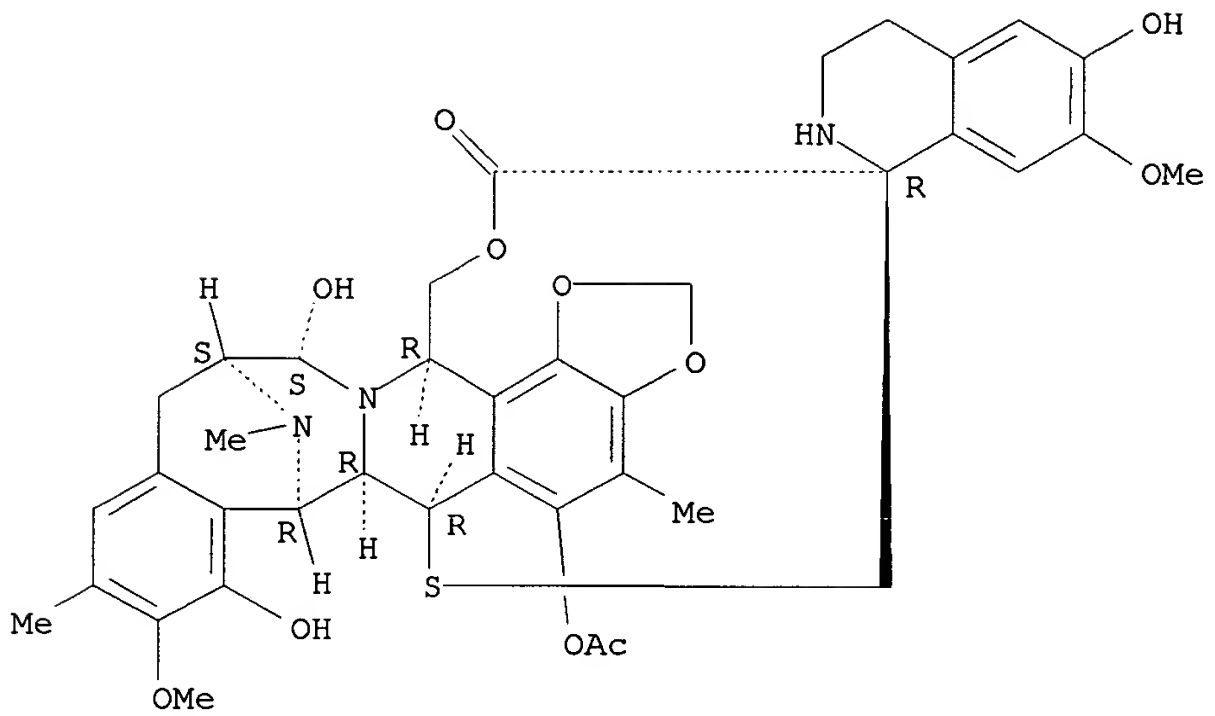
AB The use of the Staudinger ketene-imine β-lactam-forming cycloaddn.

reaction and the Pictet-Spengler cyclization reaction in sequence, was used to prepare highly functionalized tetrahydroisoquinolines, e.g. I, relevant to the bioxalomycin and ecteinascidin family of antitumor alkaloids.

REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 27 OF 76 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:83357 HCAPLUS
DOCUMENT NUMBER: 135:131682
TITLE: Pharmacokinetics and pharmacodynamics of the novel marine-derived anticancer agent ecteinascidin 743 in a phase I dose-finding study
AUTHOR(S): van Kesteren, Charlotte; Cvitkovic, Esteban; Taamma, Adelkrim; Lopez-Lazaro, Luis; Jimeno, Jose M.; Guzman, Cecilia; Mathot, Ron A. A.; Schellens, Jan H. M.; Misset, Jean-Louis; Brain, Etienne; Hillebrand, Michael J. X.; Rosing, Hilde; Beijnen, Jos H.
CORPORATE SOURCE: Department of Pharmacy and Pharmacology, Slotervaart Hospital, Amsterdam, 1066 EC, Neth.
SOURCE: Clinical Cancer Research (**2000**), 6(12), 4725-4732
CODEN: CCREF4; ISSN: 1078-0432
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **114899-77-3**, ecteinascidin 743
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(pharmacokinetics and pharmacodynamics of novel marine-derived anticancer agent ecteinascidin in humans)
RN 114899-77-3 HCAPLUS
CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



AB Ecteinascidin (ET) 743 is an anticancer agent derived from the Caribbean tunicate Ecteinascidia turbinata. Preclin. studies revealed activity of ET-743 against different tumor types. A Phase I clin. trial was designed with ET-743 to identify the maximum tolerated dose and dose-limiting toxicities (DLTs). Furthermore, the pharmacokinetics of ET-743 and relationships with pharmacodynamics were evaluated. Adult patients with solid, resistant tumors received ET-743 as a 24-h i.v. infusion every 21 days. Blood samples were obtained during the first treatment course and in several consecutive courses. Noncompartmental pharmacokinetic anal. was performed. Relationships between pharmacokinetics and hepatic and hematol. toxicities were explored. Fifty-two patients were treated at nine dose levels (50-1800 μg/m2). The DLTs, neutropenia and thrombocytopenia, were experienced at 1800 μg/m2. Twenty-five patients were treated at the recommended Phase II dose of 1500 μg/m2. At this dose, the mean value ± SD for total body clearance was 59±31 L/h, and the mean t1/2 was 89±41 h. Pharmacokinetics were linear over the dose range tested. Prior exposure to ET-743 did not alter the pharmacokinetics in subsequent courses. The percentage of decrease in WBC count and absolute neutrophil count was correlated to the area under the plasma concentration vs. time curve (AUC). Hepatic toxicity, defined as rise in alanine aminotransferase and aspartate aminotransferase, increased with dose and AUC but was reversible and not dose limiting. In conclusion, ET-743 administered as a 24-h i.v. infusion at a dose of 1500 μg/m2 is clin. feasible; severe thrombocytopenia and neutropenia are the DLTs.

REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 28 OF 76 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:73747 HCAPLUS
DOCUMENT NUMBER: 135:116666
TITLE: Ecteinascidin-743 (ET-743), a natural marine compound, with a unique mechanism of action
AUTHOR(S): Erba, E.; Bergamaschi, D.; Bassano, L.; Damia, G.; Ronzoni, S.; Faircloth, G. T.; D'Incalci, M.
CORPORATE SOURCE: Istituto di Ricerche Farmacologiche 'Mario Negri',

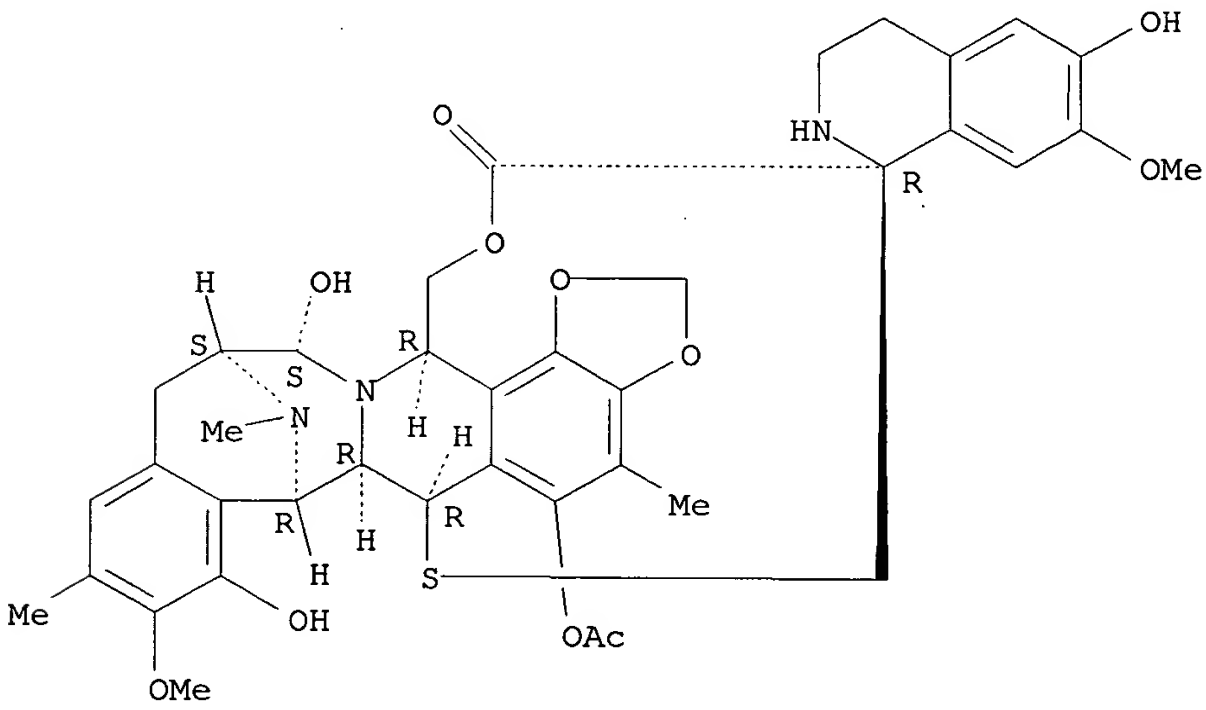
Department of Oncology, Milan, 20157, Italy
SOURCE: European Journal of Cancer (**2001**), 37(1), 97-105
CODEN: EJCAEL; ISSN: 0959-8049
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **114899-77-3**, ET-743
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(Ecteinascidin-743 (ET-743), a natural marine compound, with a unique mechanism of action)

RN 114899-77-3 HCAPLUS

CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



AB The mode of action of Ecteinascidin-743 (ET-743), a marine tetrahydroisoquinoline alkaloid isolated from Ecteinascidia turbinata, which has shown very potent antitumor activity in preclin. systems and encouraging results in Phase I clin. trials was investigated at a cellular level. Both SW620 and LoVo human intestinal carcinoma cell lines exposed for 1 h to ET-743 progress through S phase more slowly than control cells and then accumulate in the G2M phase. The sensitivity to ET-743 of G1 synchronized cells was much higher than that of cells synchronized in S phase and even higher than that of cells synchronized in G2M. ET-743 concns. up to four times higher than the IC50 value caused no detectable DNA breaks or DNA-protein cross-links as assessed by alkaline elution techniques. ET-743 induced a significant increase in p53 levels in cell lines expressing wild-type (wt) (p53). However, the p53 status does not appear to be related to the ET-743 cytotoxic activity as demonstrated by comparing the drug sensitivity in p53 (-/-) or (+/+) mouse embryo

fibroblasts and in A2780 ovarian cancer cells or the A2780/CX3 sub-line transfected with a dominant-neg. mutant TP53. The cytotoxic potency of ET-743 was comparatively evaluated in CHO cell lines proficient or deficient in nucleotide excision repair (NER), and it was found that ET-743 was approx. 7-8 times less active in ERCC3/XPB and ERCC1-deficient cells than control cells. The findings that G1 phase cells are hypersensitive and that NER-deficient cells are resistant to ET-743 indicate that the mode of action of ET-743 is unique and different from that of other DNA-interacting drugs.

REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 29 OF 76 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:824110 HCAPLUS
DOCUMENT NUMBER: 133:359227
TITLE: Compositions and uses of ET743 for treating cancer
INVENTOR(S): Bowman, Angela; Cvitkovic, Esteban; Demetri, George Daniel; Guzman, Cecilia; Jimeno, Jose; Lopez Lazaro, Luis; Misset, Jean Louis; Twelves, C.; Von Hoff, Daniel D.
PATENT ASSIGNEE(S): Pharma Mar, S.A., Spain
SOURCE: PCT Int. Appl., 30 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000069441	A1	20001123	WO 2000-GB1857	20000515 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1176964	A1	20020206	EP 2000-927584	20000515
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
BR 2000010531	A	20020604	BR 2000-10531	20000515
JP 2002544231	T2	20021224	JP 2000-617900	20000515
NO 2001005516	A	20020111	NO 2001-5516	20011112
BG 106171	A	20020628	BG 2001-106171	20011203

PRIORITY APPLN. INFO.:

GB 1999-11183	A	19990513
GB 1999-11346	A	19990514
GB 1999-18534	A	19990805
GB 1999-27005	A	19991115
GB 1999-27106	A	19991116
GB 2000-7637	A	20000329
WO 2000-GB1857	W	20000515

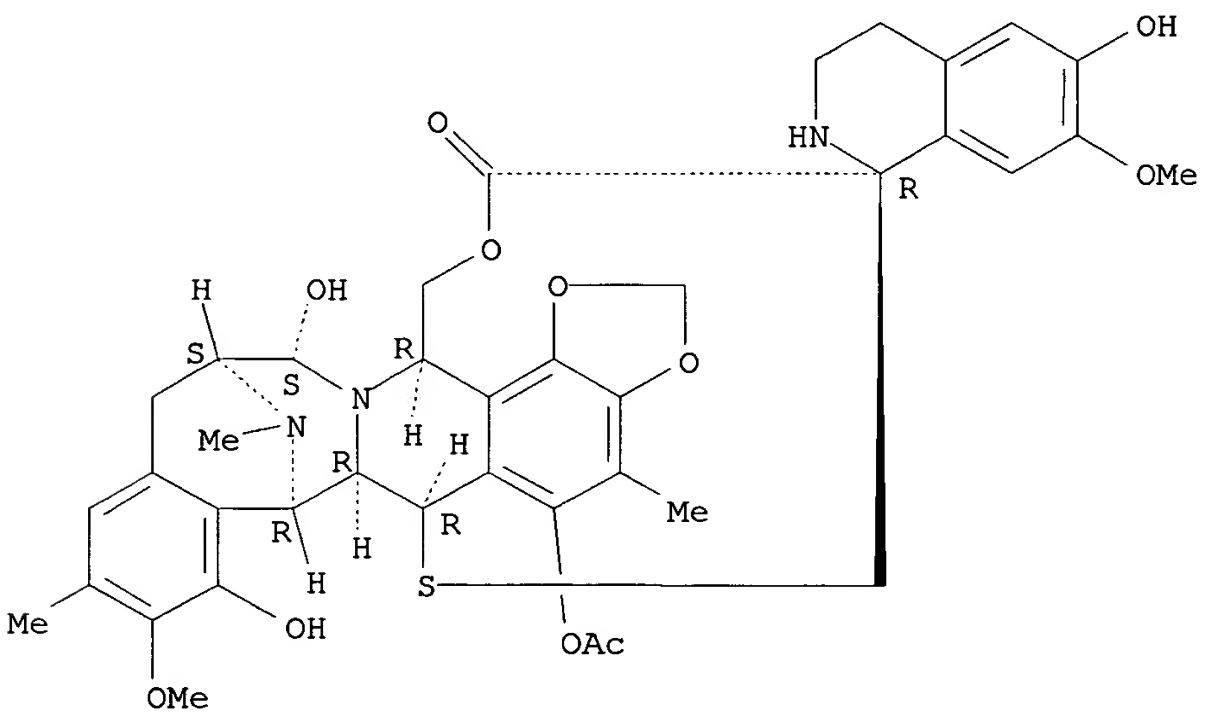
IT **114899-77-3**, Et 743
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(Et 743; i.v. infusions of ET743 for cancer treatment)

RN 114899-77-3 HCAPLUS

CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



AB ET743 is used in the preparation of a medicament for the treatment of the human body for cancer. A pharmaceutical formulation comprising ET743 for i.v. infusion is administered at 1000-1500 μg/m2 of body surface over a period of 24 h given in multiple cycles of 3-4 wk each with a single administration of the drug on the first day of each cycle.

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 30 OF 76 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2000:758606 HCAPLUS

DOCUMENT NUMBER: 134:65777

TITLE: Increased DNA Binding Specificity for Antitumor Ecteinascidin 743 through Protein-DNA Interactions?

AUTHOR(S): Garcia-Nieto, Raquel; Manzanares, Ignacio; Cuevas, Carmen; Gago, Federico

CORPORATE SOURCE: Departamento de Farmacologia, Universidad de Alcala, Madrid, E-28871, Spain

SOURCE: Journal of Medicinal Chemistry (**2000**), 43(23), 4367-4369
CODEN: JMCMAR; ISSN: 0022-2623

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

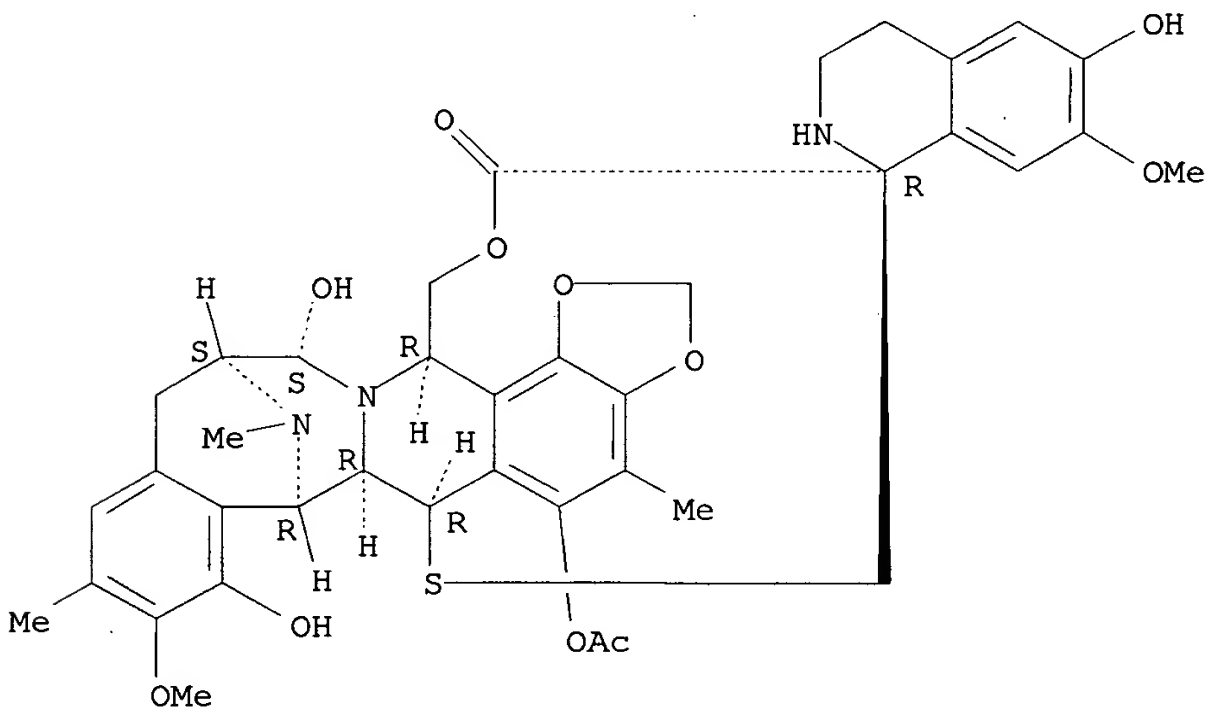
IT **114899-77-3**, Ecteinascidin 743
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)

(increased DNA binding specificity for antitumor ecteinascidin 743 through protein-DNA interactions for example transcription factors containing zinc finger motifs such as Sp1 and EGR-1.)

RN 114899-77-3 HCAPLUS

CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



AB The hypothesis is put forward that the interaction of ecteinascidin 743 (ET743) with DNA is influenced by the interactions of protein transcription factors which contain zinc finger motifs such as Sp1 and EGR-1 with DNA. Thus, ET743 binding to DNA would depend not only on the well-defined hydrogen-bonding rules necessary for sequence recognition and adduct formation, but also on the protein-induced preorganization of a DNA stretch that becomes structurally complementary to the wedge shape of the drug mol.

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 31 OF 76 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2000:755955 HCAPLUS

DOCUMENT NUMBER: 134:99596

TITLE: Aquacultural production of bryostatin 1 and ecteinascidin 743

AUTHOR(S): Mendola, Dominick

CORPORATE SOURCE: CalBioMarine Technologies, Inc., Carlsbad, CA, USA

SOURCE: Drugs from the Sea (**2000**), 120-133. Editor(s): Fusetani, Nobuhiro. S. Karger AG: Basel, Switz. CODEN: 69ANZX

DOCUMENT TYPE: Conference; General Review

LANGUAGE: English

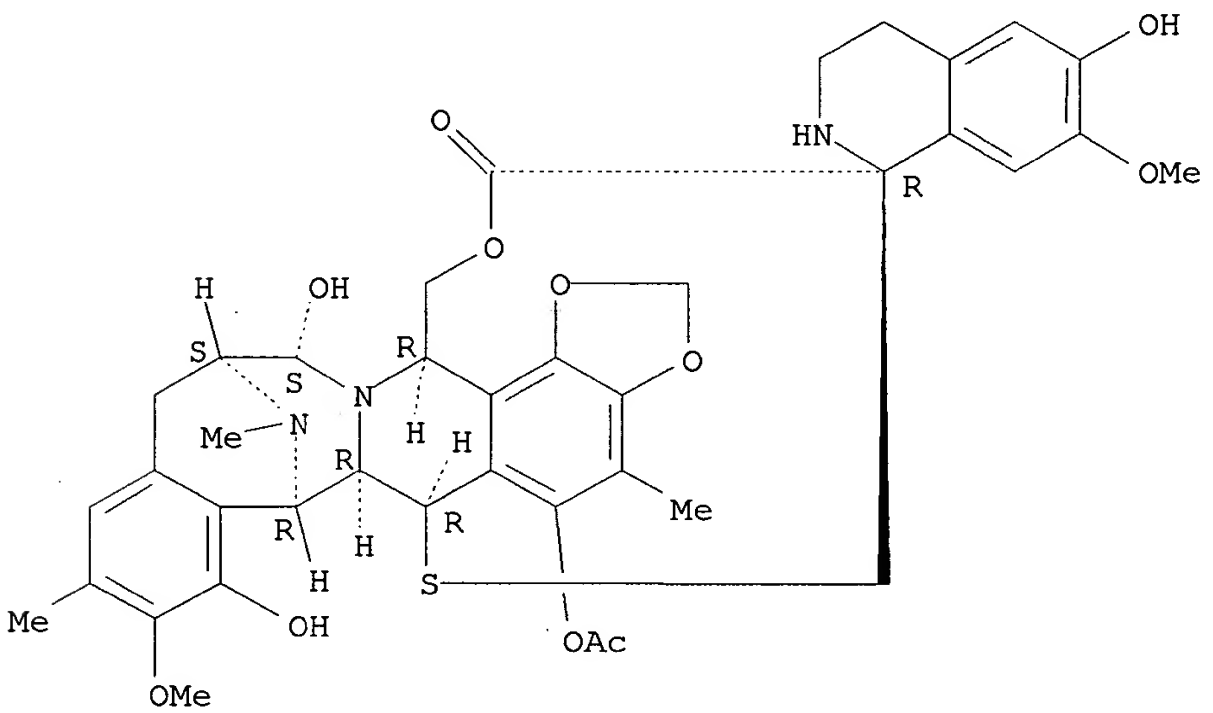
IT **114899-77-3P**, Ecteinascidin 743

RL: BMF (Bioindustrial manufacture); BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)
(aquacultural production of bryostatin 1 and ecteinascidin 743)

RN 114899-77-3 HCAPLUS

CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



AB A review with 12 refs. regarding the aquacultural production of bryostatin 1 and ecteinascidin 743. Two case studies are presented which chronicle the development of such aquaculture systems. Both technologies are now in the prototype testing phases of their development.

REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 32 OF 76 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2000:734389 HCAPLUS

DOCUMENT NUMBER: 134:29602

TITLE: A practical synthesis of the ABC ring model of ecteinascidins

AUTHOR(S): Saito, Naoki; Tachi, Masashi; Seki, Ryu-Ichi; Kamayachi, Hiroshi; Kubo, Akinori

CORPORATE SOURCE: Meiji Pharmaceutical University, Tokyo, 204-8588, Japan

SOURCE: Chemical & Pharmaceutical Bulletin (**2000**), 48(10), 1549-1557
CODEN: CPBTAL; ISSN: 0009-2363

PUBLISHER: Pharmaceutical Society of Japan

DOCUMENT TYPE: Journal

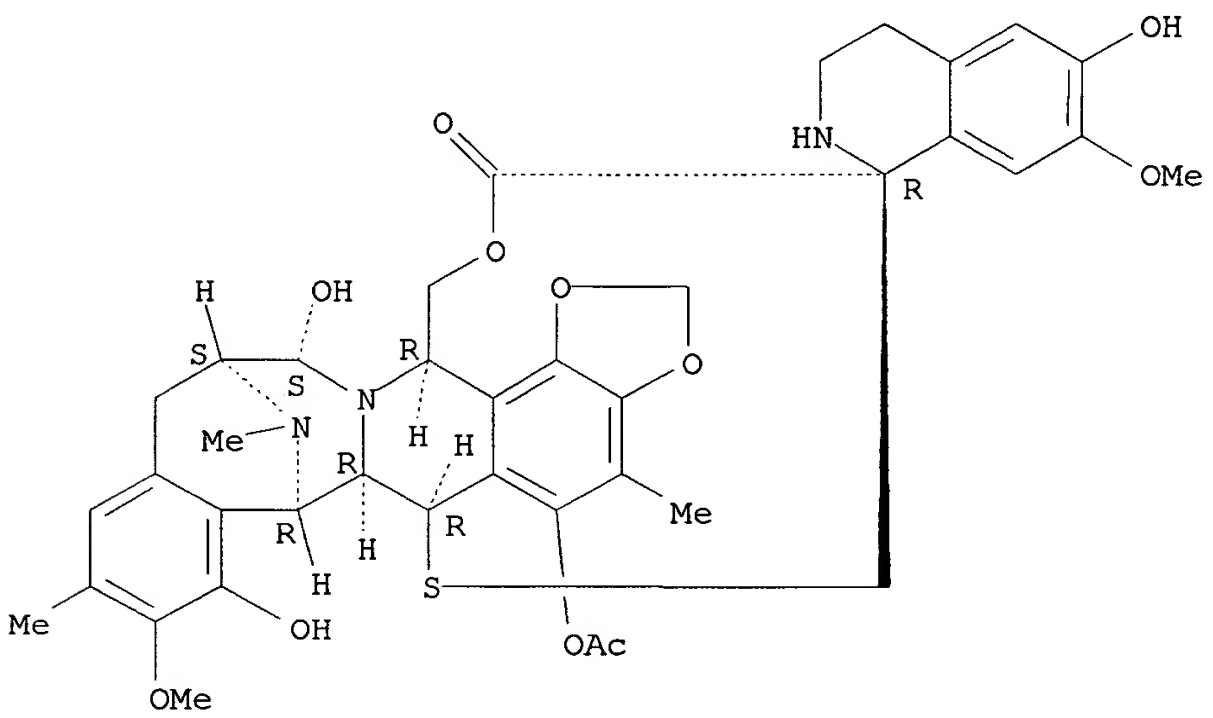
LANGUAGE: English

OTHER SOURCE(S): CASREACT 134:29602

IT **114899-77-3P**, Ecteinascidin 743
RL: PNU (Preparation, unclassified); PREP (Preparation)

(synthesis of the ABC ring model of ecteinascidins)
RN 114899-77-3 HCAPLUS
CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

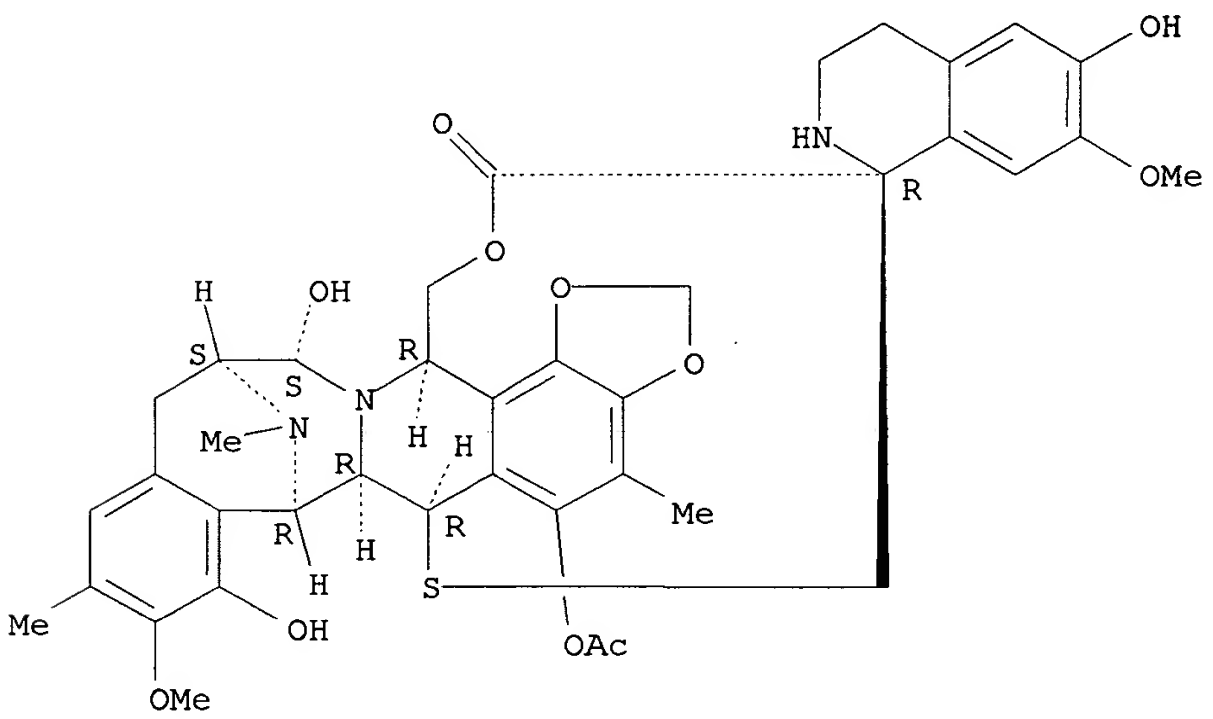


AB A practical synthesis of 1,2,3,4,5,6-hexahydro-1,5-imino-10-hydroxy-9-methoxy-3,8,11-trimethyl-3-benzazocin-4-one as an ABC ring model compound of ecteinascidin 743 and safracins from 3-hydroxy-4-methoxy-5-methylbenzaldehyde is described. The overall yield in 15 steps is 27%.
REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 33 OF 76 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:489993 HCAPLUS
DOCUMENT NUMBER: 133:222874
TITLE: Synthesis of Ecteinascidin ET-743 and Phthalascidin Pt-650 from Cyanosafracin B
AUTHOR(S): Cuevas, Carmen; Perez, Marta; Martin, Maria J.; Chicharro, Jose L.; Fernandez-Rivas, Carolina; Flores, Maria; Francesch, Andres; Gallego, Pilar; Zarzuelo, Maria; de la Calle, Fernando; Garćia, Jesus; Polanco, Concepcion; Rodriguez, Ignacio; Manzanares, Ignacio
CORPORATE SOURCE: Pharma Mar, Madrid, 28760, Spain
SOURCE: Organic Letters (**2000**), 2(16), 2545-2548
CODEN: ORLEF7; ISSN: 1523-7060
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **114899-77-3P**, Ecteinascidin 743
RL: SPN (Synthetic preparation); PREP (Preparation)
(synthesis of ecteinascidin ET-743 and phthalascidin Pt-650 from cyanosafracin B)

RN 114899-77-3 HCAPLUS
CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

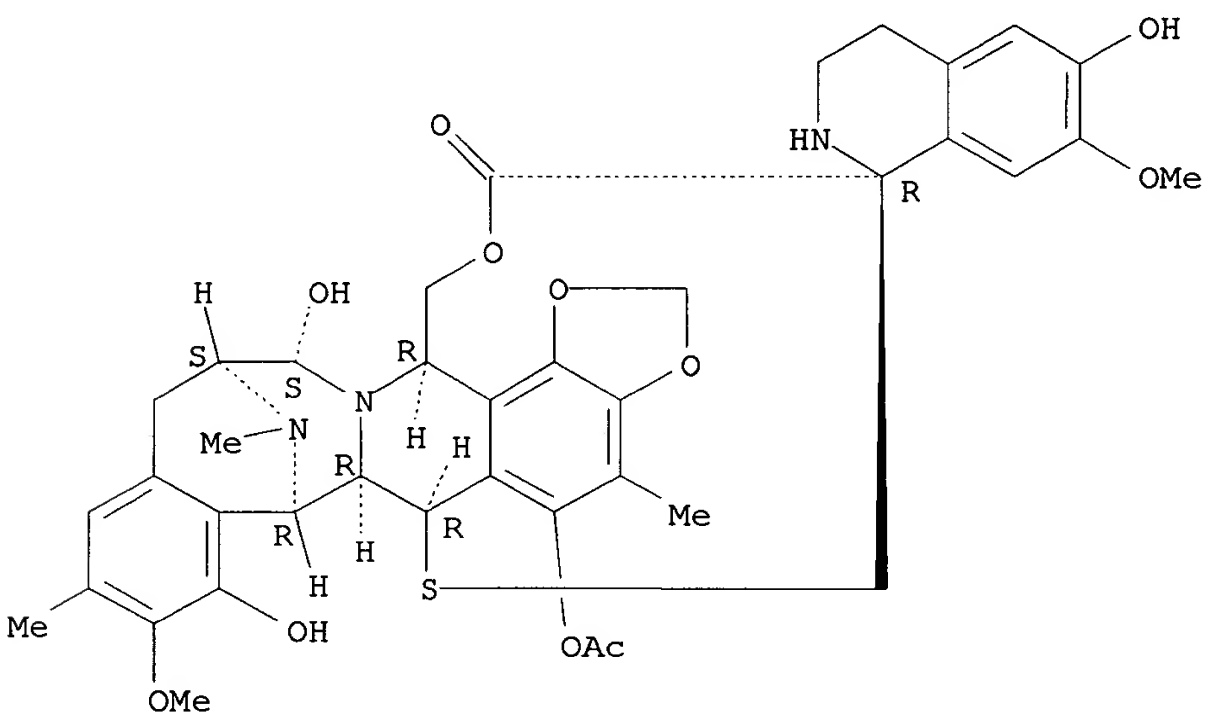


AB An efficient new process is described for the synthesis of ecteinascidin ET-743 and phthalascidin, starting from readily available cyanosafracin B.
REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 34 OF 76 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:471539 HCAPLUS
DOCUMENT NUMBER: 133:217353
TITLE: Bending of DNA upon binding of ecteinascidin 743 and phthalascidin 650 studied by unrestrained molecular dynamics simulations
AUTHOR(S): Garcia-Nieto, Raquel; Manzanares, Ignacio; Cuevas, Carmen; Gago, Federico
CORPORATE SOURCE: Departamento de Farmacologia, Universidad de Alcala, Madrid, 28760, Spain
SOURCE: Journal of the American Chemical Society (**2000**), 122(30), 7172-7182
CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **114899-77-3**, Ecteinascidin 743
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(complexes with DNA; bending of DNA upon binding of ecteinascidin 743 and phthalascidin 650 studied by unrestrained mol. dynamics simulations)

RN 114899-77-3 HCAPLUS
CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

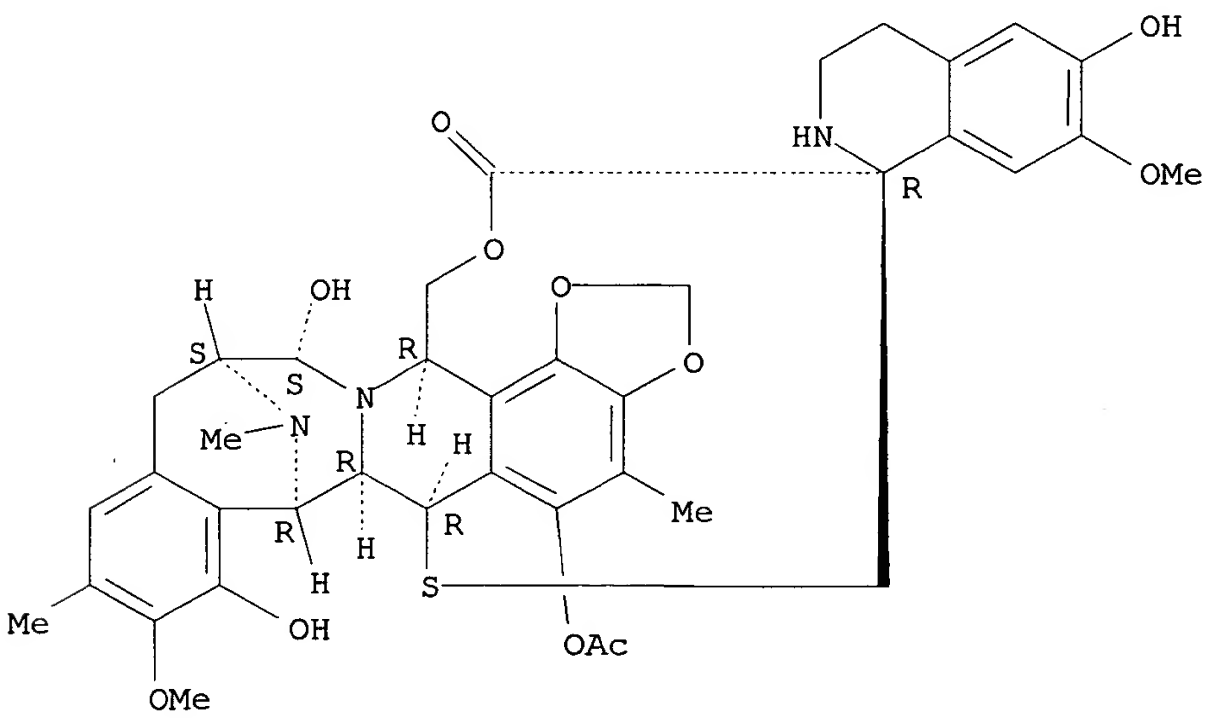


AB Recognition of DNA sequence information by the natural antitumor agent ecteinascidin 743 (ET743) has been proposed to operate through a direct readout mechanism involving specific hydrogen bonding interactions between the drug and the DNA minor groove prior to covalent alkylation of a guanine base. 5'-AGC and 5'-CGG are examples of high-reactivity target triplets whereas 5'-CGA is a low-reactivity sequence. Mol. dynamics computer simulations were first used to explore the stability and behavior of the pre-covalent complex between ET743 and a DNA nonamer containing the 5'-AGC binding site in the central region. The pre-covalent complex was stable, and some unreported distinctive features were observed that may not be amenable to direct exptl. verification. A similar simulation with ET743 bound to another nonamer containing a central 5'-CGA triplet did not result in a stable association supporting the proposed role of a hydrogen bonding network in the stabilization of these complexes. The covalent complexes between ET743 and the nonamers containing the 5'-AGC and 5'-CGG target sites were then simulated. In each case the drug displayed the predicted binding mode and gave rise to a widening of the minor groove. In addition, we show that as a consequence of ET743 binding to the target sequences, pos. roll is introduced that results in smooth bending of the helix toward the major groove, in agreement with results from gel electrophoresis expts. Similar results were obtained with the synthetic compound phthalascidin, which presents a biol. profile almost indistinguishable from that of ET743. The local bending elements in AGC and CGG were found to be different, and the distinct behavior of these sequences in the absence of bound drugs was in consonance with their intrinsic bending propensities.

REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 35 OF 76 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:412188 HCAPLUS
DOCUMENT NUMBER: 133:129636
TITLE: Interference of transcriptional activation by the antineoplastic drug ecteinascidin-743
AUTHOR(S): Minuzzo, Mario; Marchini, Sergio; Broggini, Massimo; Faircloth, Glynn; D'Incalci, Maurizio; Mantovani, Roberto
CORPORATE SOURCE: Dipartimento di Genetica e di Biologia dei Microrganismi, Universita degli Studi di Milano, Milan, 20133, Italy
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (**2000**), 97(12), 6780-6784
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **114899-77-3**, Ecteinascidin-743
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(interference of transcriptional activation by antineoplastic drug ecteinascidin-743 at HSP70 promoter in relation to binding by CCAAT box factor NF-Y and heat-shock factor)
RN 114899-77-3 HCAPLUS
CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



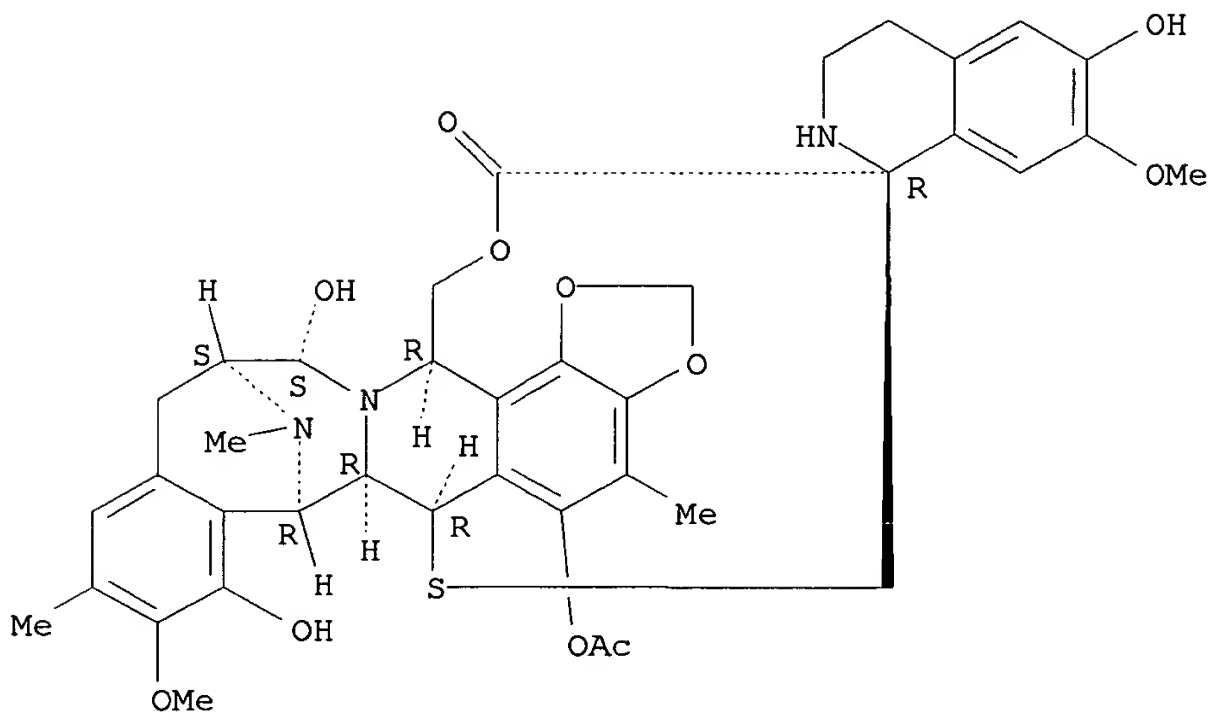
AB Ecteinascidin-743 (ET-743) is a tetrahydroisoquinoline alkaloid isolated from the tunicate Ecteinascidia turbinata currently under phase II clin.

trials for its potent anticancer activity. ET-743 binds DNA in the minor groove and forms covalent adducts with some sequence specificity. It selectively inhibits in vitro binding of the CCAAT box factor NF-Y. In this study, the authors assayed ET-743 function in vivo on the HSP70 promoter. On heat induction, the drug blocks transcription rapidly at pharmacol. concns. and in a CCAAT-dependent manner, whereas the activity of the CCAAT-less simian virus 40 promoter is not affected. The effect is exerted at the mRNA level. The distamycin-like alkylating tallimustine is inactive in these assays. Binding of NF-Y and of the heat-shock factor is normal in ET-743-treated cells. Run-on anal. of several endogenous genes further proves that the drug has rapid, profound, and selective neg. effects on transcription. Thus, this marine-derived compound is a promoter-specific, transcription-interfering agent.

REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 36 OF 76 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:412185 HCAPLUS
DOCUMENT NUMBER: 133:129635
TITLE: Ecteinascidin 743, a transcription-targeted chemotherapeutic that inhibits MDR1 activation
AUTHOR(S): Jin, Shengkan; Gorfajn, Barbara; Faircloth, Glynn; Scotto, Kathleen W.
CORPORATE SOURCE: Molecular Pharmacology and Therapeutics Program, Memorial Sloan-Kettering Cancer Center and the Weill Graduate School of Medical Sciences of Cornell University, New York, NY, 10021, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (**2000**), 97(12), 6775-6779
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **114899-77-3**, Ecteinascidin 743
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ecteinascidin 743 as transcription-targeted antitumor chemotherapeutic that inhibits MDR1 promoter activation in relation to NF-Y/PCAF complex and histone hyperacetylation)
RN 114899-77-3 HCAPLUS
CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



AB Ecteinascidin 743 (ET-743), a highly promising marine-based anti-tumor agent presently in phase II clin. trials, has been shown to interfere with the binding of minor-groove-interacting transcription factors, particularly NF-Y, with their cognate promoter elements in vitro. The authors have shown that NF-Y is a central mediator of activation of transcription of the human P glycoprotein gene (MDR1) by a variety of inducers and that NF-Y functions by recruiting the histone acetyltransferase PCAF to the MDR1 promoter. In the present study, the authors tested whether ET-743 could block activation of the MDR1 promoter by agents that mediate their effect through the NF-Y/PCAF complex. The authors report that physiol. relevant concns. of ET-743 abrogate transcriptional activation of both the endogenous MDR1 gene and MDR1 reporter constructs by the histone deacetylase inhibitors as well as by UV light, with minimal effect on constitutive MDR1 transcription. Notably, this inhibition does not alter the promoter-associated histone hyperacetylation induced by histone deacetylase inhibitors, suggesting an in vivo mol. target downstream of NF-Y/PCAF binding. ET-743 is therefore the prototype for a distinct class of transcription-targeted chemotherapeutic agents and may be an efficacious adjuvant to the treatment of multidrug-resistant tumors.

REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 37 OF 76 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:402043 HCAPLUS
DOCUMENT NUMBER: 133:26835
TITLE: Toxicity typing using embryoid bodies
INVENTOR(S): Snodgrass, H. Ralph
PATENT ASSIGNEE(S): Vistagen, Inc., USA
SOURCE: PCT Int. Appl., 56 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000034525	A1	20000615	WO 1999-US29384	19991209 <--
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1137809	A1	20011004	EP 1999-963069	19991209 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002531852	T2	20020924	JP 2000-586957	19991209
US 2001039006	A1	20011108	US 2001-864621	20010523 <--

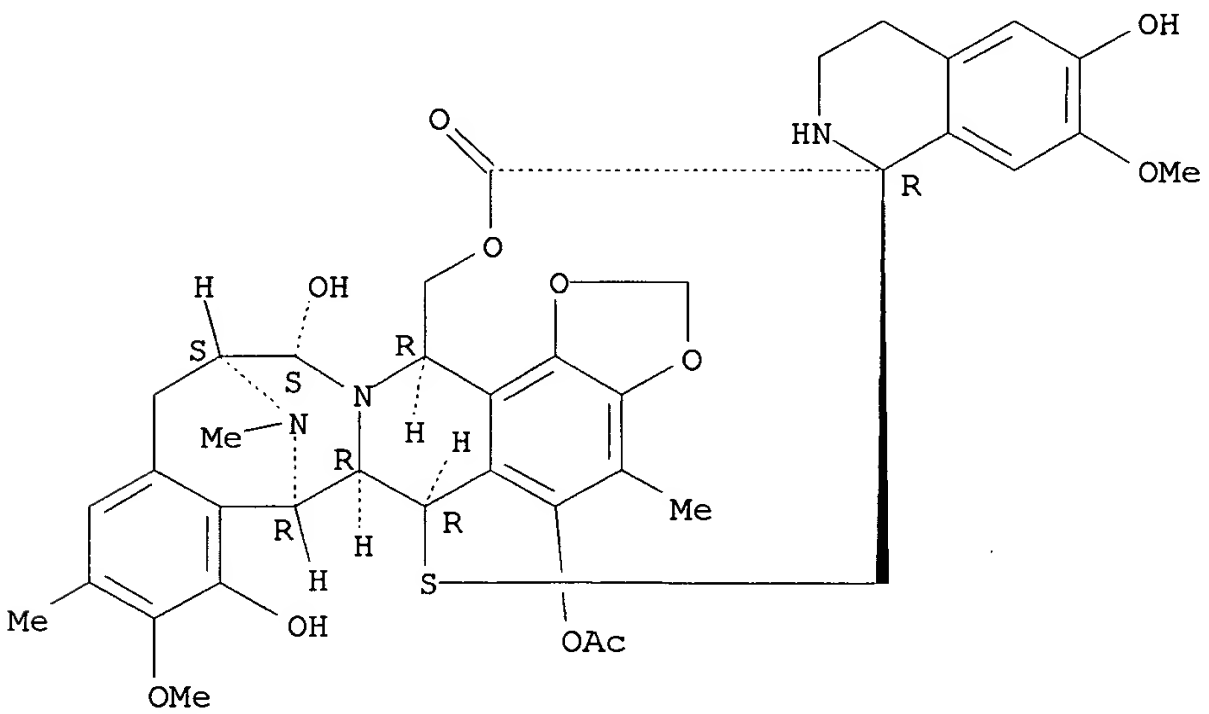
PRIORITY APPLN. INFO.:			
US 1998-111640P	P	19981209	
US 1999-457931	A	19991208	
WO 1999-US29384	W	19991209	

IT **114899-77-3**, Ecteinascidin 743
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study) (toxicity typing using embryoid bodies)

RN 114899-77-3 HCAPLUS

CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



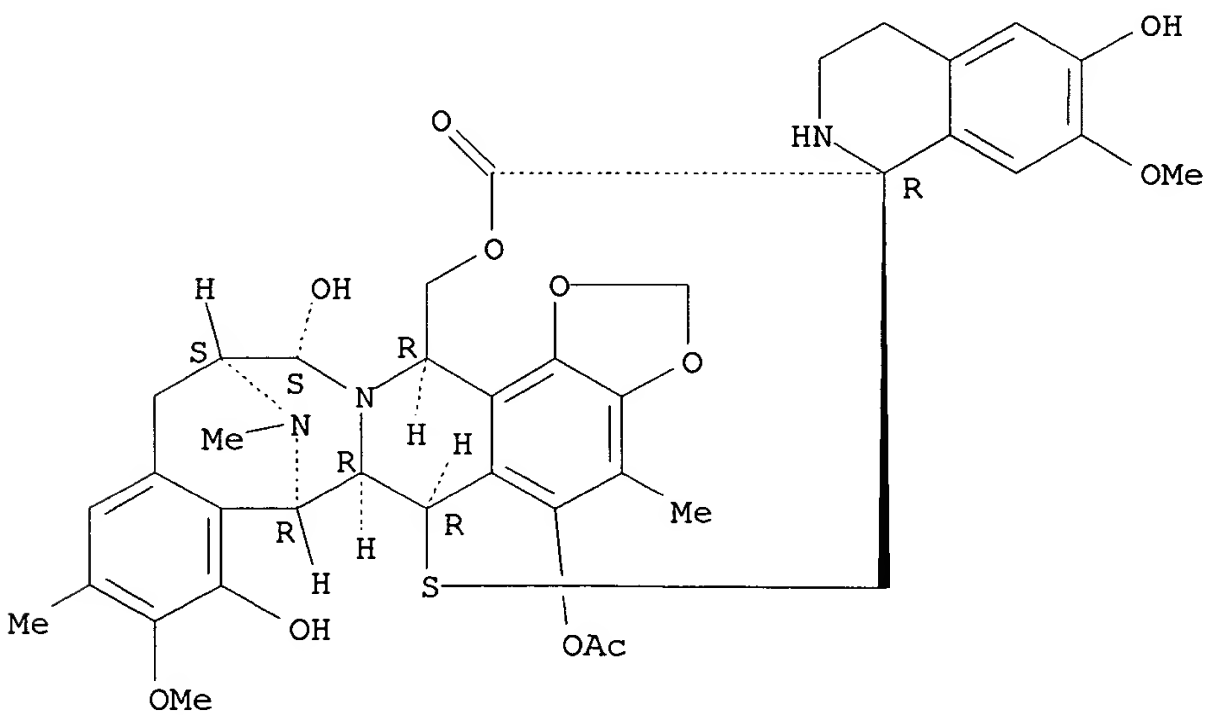
AB This invention provides methods and systems for identifying and typing toxicity of chemical compns., as well as for screening new compns. for toxicity. The invention involves detecting alterations in gene or protein expression and hence establishing mol. profiles in isolated mammalian embryoid bodies contacted with various chemical compns. of known and unknown

toxicities, and correlating the mol. profiles with toxicities of the chemical compns.

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 38 OF 76 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:384338 HCAPLUS
DOCUMENT NUMBER: 133:217447
TITLE: Isolation and characterization of an IGROV-1 human ovarian cancer cell line made resistant to Ecteinascidin-743 (ET-743)
AUTHOR(S): Erba, E.; Bergamaschi, D.; Bassano, L.; Ronzoni, S.; Di Liberti, G.; Muradore, I.; Vignati, S.; Faircloth, G.; Jimeno, J.; D'Incalci, M.
CORPORATE SOURCE: Cancer Pharmacology Laboratory, Department of Oncology, Istituto di Ricerche Farmacologiche "Mario Negri", Milan, 62-20157, Italy
SOURCE: British Journal of Cancer (**2000**), 82(10), 1732-1739
CODEN: BJCAAI; ISSN: 0007-0920
PUBLISHER: Harcourt Publishers Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **114899-77-3**, Ecteinascidin-743
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(isolation and characterization of an IGROV-1 human ovarian cancer cell line made resistant to Ecteinascidin-743 (ET-743))
RN 114899-77-3 HCAPLUS
CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

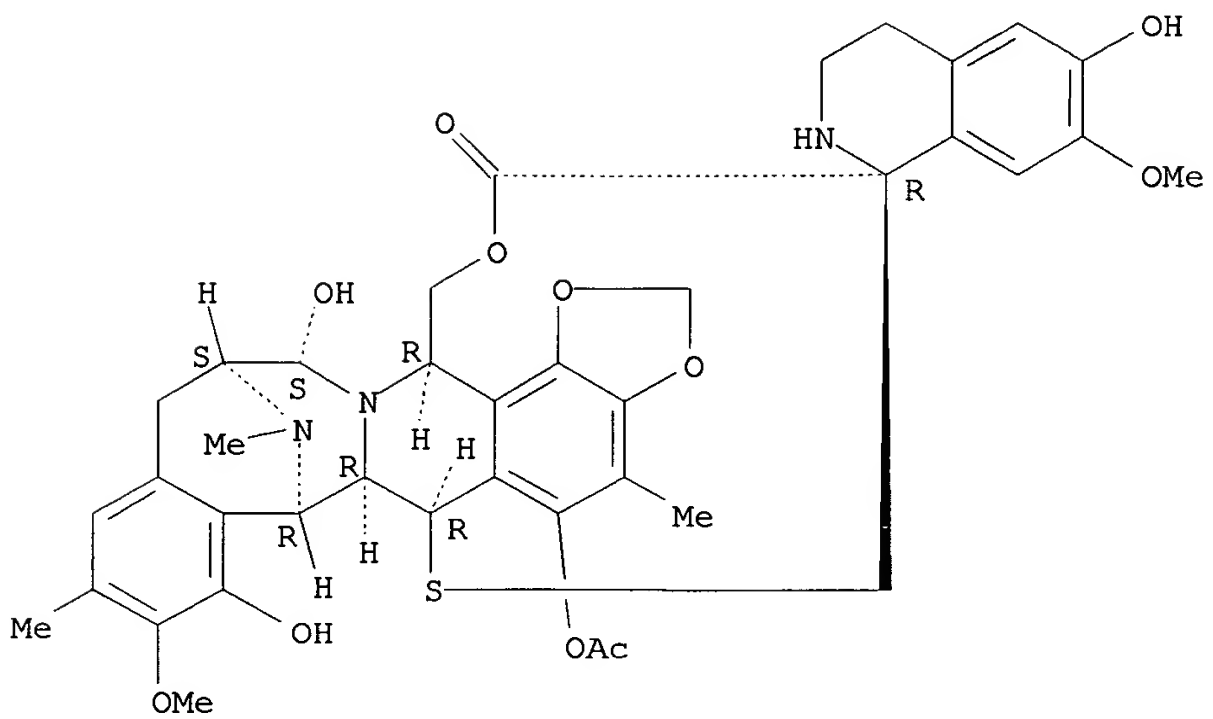


AB By exposing Igrov-1 human ovarian cancer cells to increasing concns. of Ecteinascidin-743 (ET-743), either for a short or prolonged time, the authors obtained sublines resistant to ET-743 which overexpress Pgp. The most resistant clone (Igrov-1/25 ET) was evaluated for biol. and pharmacol. characterizations. The increased Pgp levels of Igrov-1/25 ET were not due to amplification of the mdr-1 gene but to increased mRNA levels. No increase in other multidrug resistance-related proteins such as MRP or LRP was observed in Igrov-1/25 ET. The IC50 values of ET-743 against Igrov-1/25 ET was approx. 50 times higher than the parental cell line. Resistance was not reversed while maintaining the cell line in drug-free medium for at least 24 mo. Igrov-1/25 ET was cross-resistant to doxorubicin and VP 16 while it was equally sensitive to L-PAM, MNNG, CPT, and only marginally less sensitive to Cis-DDP and oxaliplatin compared to the parental cell line. Igrov-1/25 ET exposed to doxorubicin retained this drug much less, mainly because of a more efficient drug efflux. The cyclosporine analog SDZ PSC-833 reversed the resistance of Igrov-1/25 ET to ET-743, without any enhancement of the drug activity against the parental Igrov-1 cell line. Igrov-1/25 ET exhibits typical features of cell lines overexpressing the mdr-1 gene and can be a potentially useful tool in selecting ET-743 non-cross-resistant analogs as well as to investigate methods to counteract resistance to this drug.

REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 39 OF 76 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:373659 HCAPLUS
DOCUMENT NUMBER: 133:177467
TITLE: Diketopiperazines as advanced intermediates in the biosynthesis of ecteinascidins
AUTHOR(S): Jeedigunta, Shanti; Krenisky, Joann M.; Kerr, Russell G.
CORPORATE SOURCE: Department of Chemistry and Biochemistry, Center for Molecular Biology and Biotechnology, Florida Atlantic University, Boca Raton, FL, 33431-0991, USA
SOURCE: Tetrahedron (**2000**), 56(21), 3303-3307
CODEN: TETRAB; ISSN: 0040-4020
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **288609-53-0P**
RL: BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation of diketopiperazines of Phe, Tyr and DOPA as advanced intermediates in the biosynthesis of ecteinascidins)
RN 288609-53-0 HCAPLUS
CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, labeled with carbon-14, (1'R,6R,6aR,7R,13S,14S,16R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



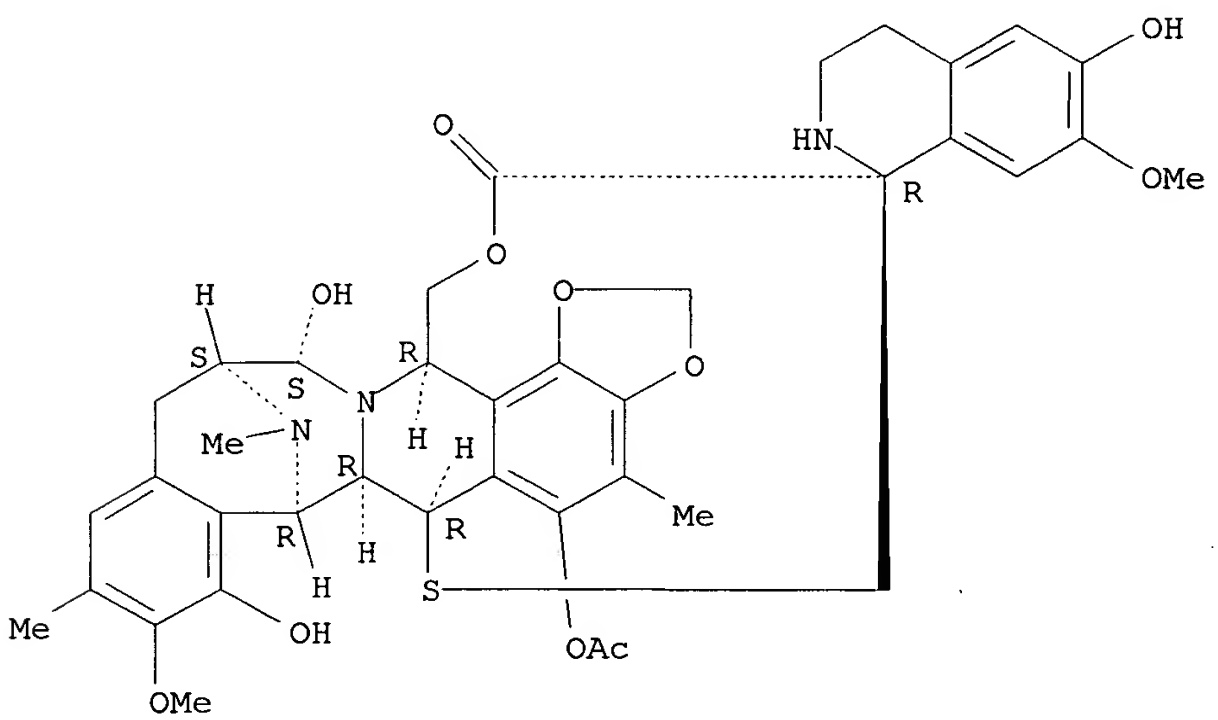
AB The diketopiperazines of L-phenylalanine, L-tyrosine and L-DOPA have been synthesized from 14C-labeled amino acids and tested as intermediates in the biosynthesis of the ecteinascidins. Biosynthetic expts. were performed using an enzyme preparation of the tunicate Ecteinascidia turbinata, the source of the ecteinascidins. Tyrosine and DOPA diketopiperazines were both transformed to the ecteinascidins whereas the diketopiperazine of phenylalanine was not modified. It is now apparent that the biosynthesis of the ecteinascidins is initiated by the condensation of tyrosine to its cyclic dipeptide followed by a subsequent oxidation to the diketopiperazine of DOPA.

REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

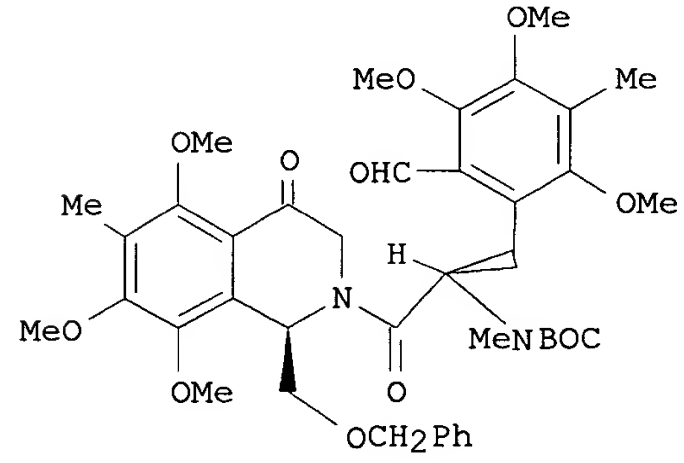
L27 ANSWER 40 OF 76 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:248566 HCAPLUS
DOCUMENT NUMBER: 133:30850
TITLE: A novel face specific Mannich closure providing access to the saframycin-ecteinascidin series of piperazine based alkaloids
AUTHOR(S): Zhou, Bishan; Guo, Jinsong; Danishefsky, Samuel J.
CORPORATE SOURCE: The Department of Chemistry, Columbia University, New York, NY, 10027, USA
SOURCE: Tetrahedron Letters (**2000**), 41(13), 2043-2046
CODEN: TELEAY; ISSN: 0040-4039
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 133:30850
IT **114899-77-3DP**, Ecteinascidin 743, derivs.
RL: PNU (Preparation, unclassified); PREP (Preparation)
(face specific Mannich closure providing access to saframycin-ecteinascidin series of piperazine based alkaloids)
RN 114899-77-3 HCAPLUS
CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one,

5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (9CI) (CA INDEX NAME)

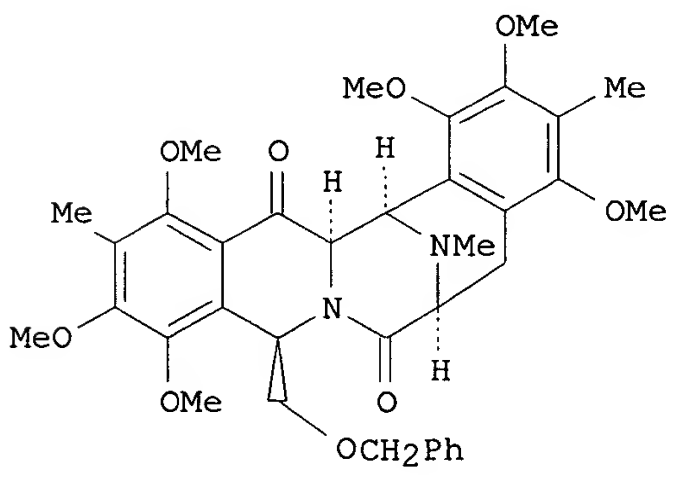
Absolute stereochemistry. Rotation (-).



GI



I

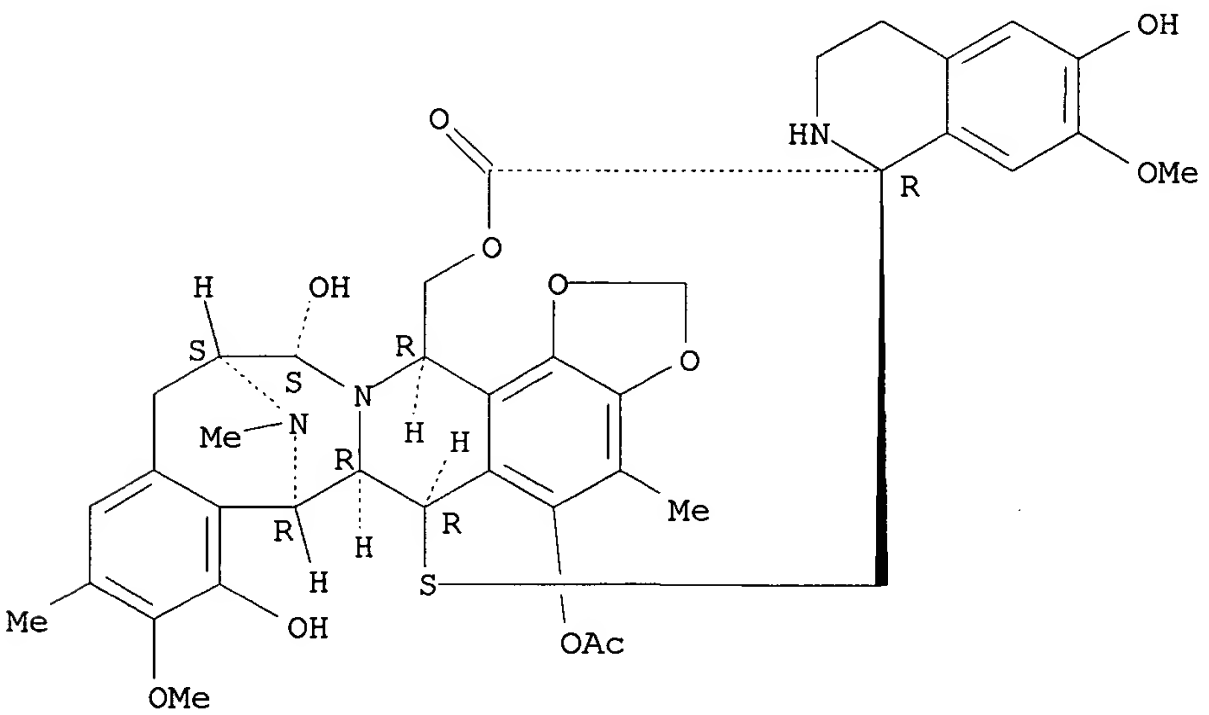


II

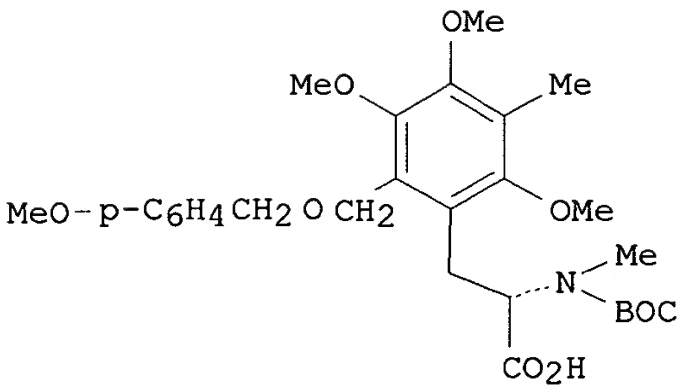
AB The Mannich-like closure of I to II directly provides the backbone stereochem. required for the titled alkaloids, in contrast to the stereochem. outcome in a related earlier case.
REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 41 OF 76 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:248565 HCAPLUS
DOCUMENT NUMBER: 133:4840
TITLE: Synthetic explorations in the saframycin-ecteinascidin series: construction of major chiral subunits through catalytic asymmetric induction
AUTHOR(S): Zhou, Bishan; Edmondson, Scott; Padron, Juan; Danishefsky, Samuel J.
CORPORATE SOURCE: The Department of Chemistry, Columbia University, New York, NY, 10027, USA
SOURCE: Tetrahedron Letters (**2000**), 41(13), 2039-2042
CODEN: TELEAY; ISSN: 0040-4039
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 133:4840
IT **114899-77-3P**, Ecteinascidin 743
RL: PNU (Preparation, unclassified); PREP (Preparation)
(construction of major chiral ecteinascidin subunits via catalytic asym. induction)
RN 114899-77-3 HCAPLUS
CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (9CI) (CA INDEX NAME)

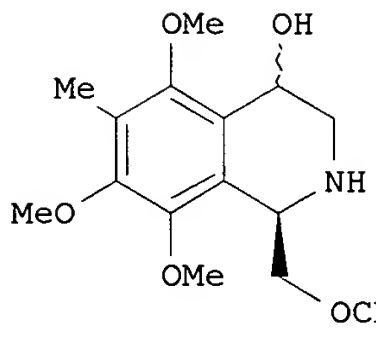
Absolute stereochemistry. Rotation (-).



GI



I



II

AB The major subunits (I and II) needed to reach the titled targets have been assembled by chemical, which included p-Claisen rearrangement, asym. epoxidn. and asym. dihydroxylation.

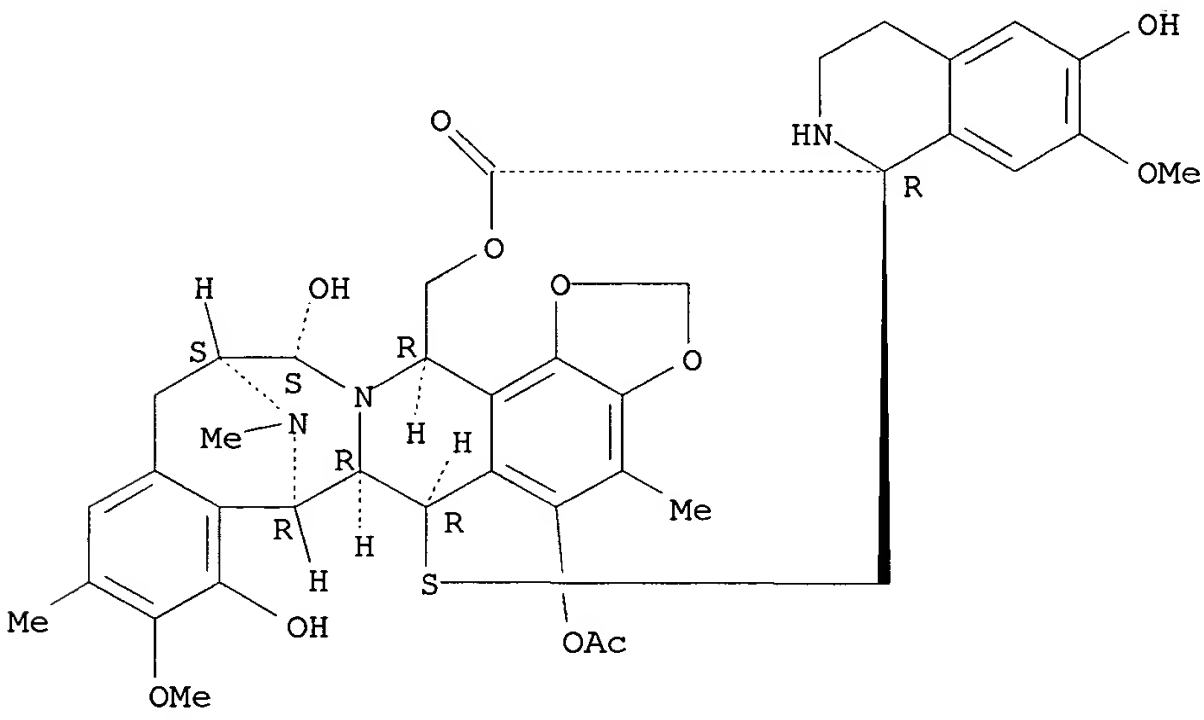
REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 42 OF 76 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:227437 HCAPLUS
DOCUMENT NUMBER: 132:251289
TITLE: Preparation of ecteinascidin 743 analogs for pharmaceutical use as antitumor agents
INVENTOR(S): Corey, Elias J.
PATENT ASSIGNEE(S): President and Fellows of Harvard College, USA
SOURCE: PCT Int. Appl., 163 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

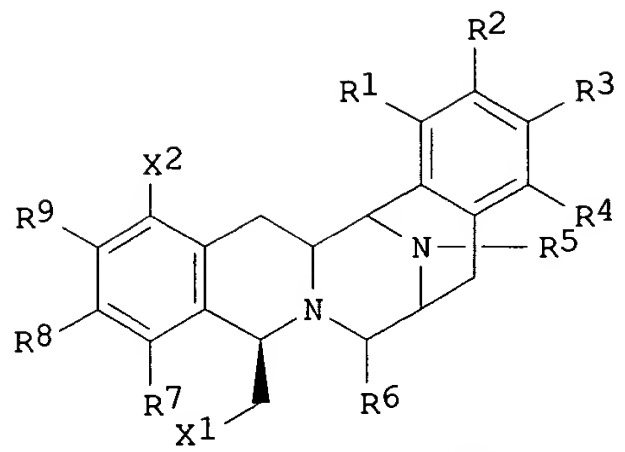
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
WO 2000018233	A1	20000406	WO 1999-US22405	19990930	<--
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG					
US 6124292	A	20000926	US 1998-165892	19980930	<--
CA 2345297	AA	20000406	CA 1999-2345297	19990930	<--
AU 9961650	A1	20000417	AU 1999-61650	19990930	<--
AU 765439	B2	20030918			
EP 1117297	A1	20010725	EP 1999-948484	19990930	<--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO					
JP 2002525296	T2	20020813	JP 2000-571761	19990930	
NZ 510734	A	20031031	NZ 1999-510734	19990930	
US 6348467	B1	20020219	US 2000-510315	20000222	

US 6569859 B1 20030527 US 2002-77700 20020214
PRIORITY APPLN. INFO.: US 1998-165892 A 19980930
WO 1999-US22405 W 19990930
US 2000-510315 A1 20000222
OTHER SOURCE(S): MARPAT 132:251289
IT **114899-77-3DP**, Ecteinascidin 743, analogs
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of ecteinascidin 743 analogs for pharmaceutical use as antitumor agents)
RN 114899-77-3 HCAPLUS
CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (9CI) (CA INDEX NAME)

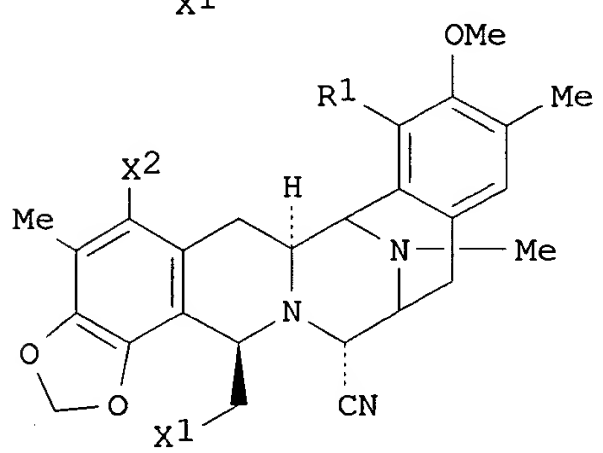
Absolute stereochemistry. Rotation (-).



GI



I



II

AB Ecteinascidin 743 analogs I [R1, R2, R3, R4, R5, R6, R7, R8, R9 = H, OH, SH, NO2, NH2, CHO, CO2H, alkyloxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, halogen, alkyl, alkenyl, alkynyl, aryl, etc.; X1, X2 = H, OH, SH, NO2, NH2, CHO, CO2H, alkyloxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, halogen, phthalimido, etc.] were prepared for use as anticancer agents. Thus, ecteinascidin 743 analogs II (R1 = OH, X1 = phthalimido, X2 = AcO) was prepared in a series of synthetic steps via coupling of phthalimide with II (R1 = MeOCH2O, X1 = OH, X2 = CH2:CHCH2O). The prepared compds. were tested for antitumor activity against a variety of cancer cell lines, such as lung, colon, prostate and melanoma.

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

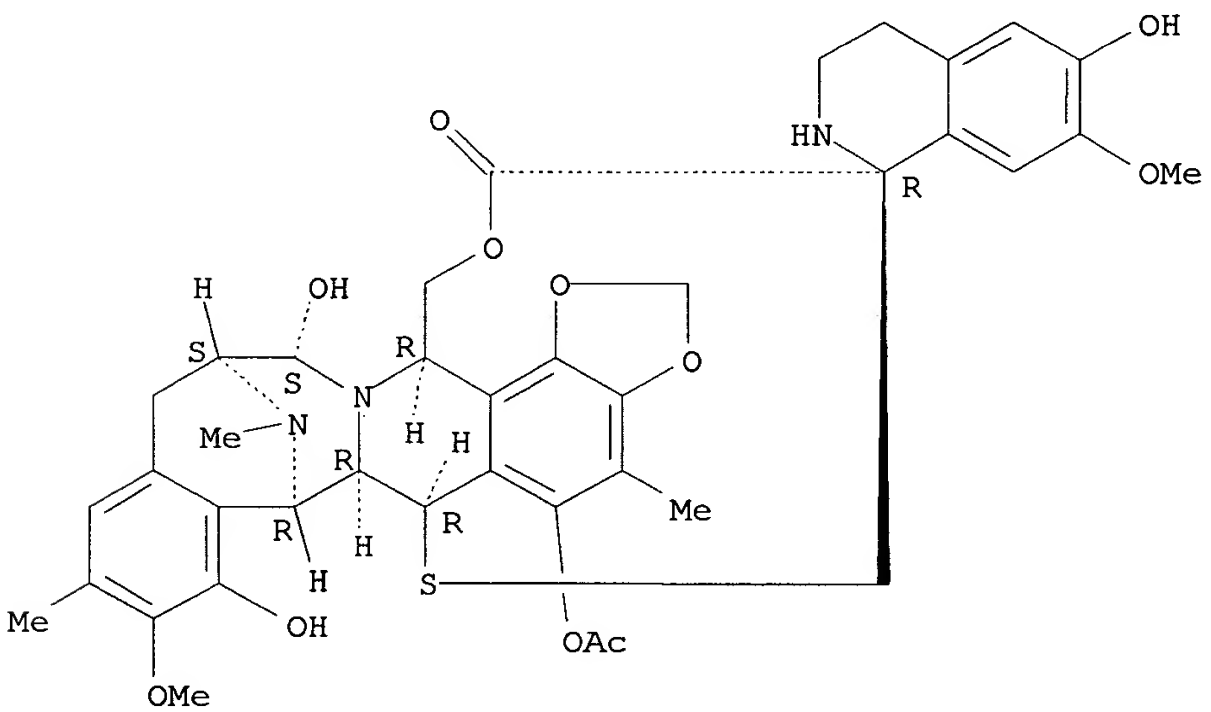
L27 ANSWER 43 OF 76 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:167657 HCAPLUS
DOCUMENT NUMBER: 132:308537
TITLE: A New, More Efficient, and Effective Process for the Synthesis of a Key Pentacyclic Intermediate for Production of Ecteinascidin and Phthalascidin Antitumor Agents
AUTHOR(S): Martinez, Eduardo J.; Corey, E. J.
CORPORATE SOURCE: Department of Chemistry, Chemical Biology Harvard University, Cambridge, MA, 02138, USA
SOURCE: Organic Letters (**2000**), 2(7), 993-996
CODEN: ORLEF7; ISSN: 1523-7060
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 132:308537
IT **114899-77-3P**, Ecteinascidin 743

RL: PNU (Preparation, unclassified); PREP (Preparation)
(synthesis of a dey pentacyclic synthetic intermediate for preparation of ecteinascidin 743 and phthalascidin)

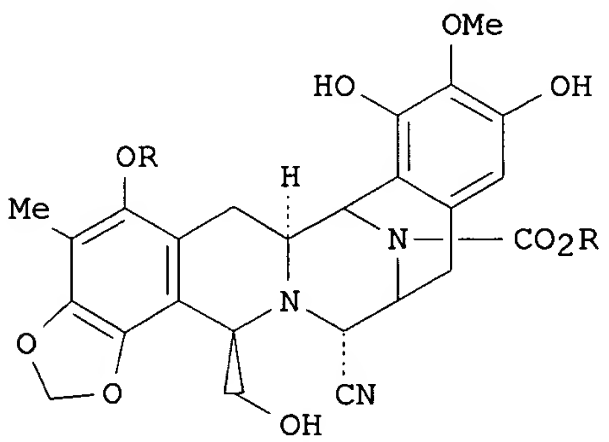
RN 114899-77-3 HCAPLUS

CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (9CI) (CA INDEX NAME)

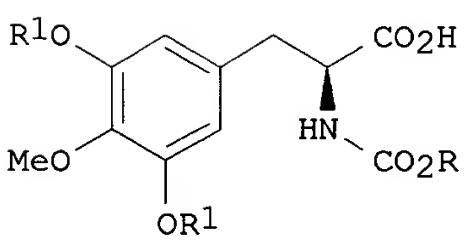
Absolute stereochemistry. Rotation (-).



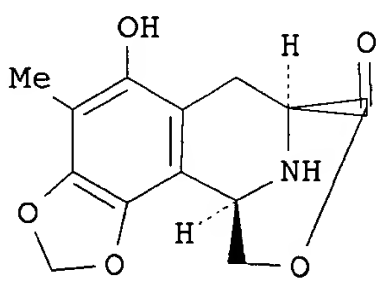
GI



I



II



III

AB An efficient process was described for the synthesis of I (R = allyl), a key intermediate for the synthesis of the potent antitumor agents ecteinascidin 743 and phthalascidin, which started from the readily available building blocks II (R = allyl, R1 = SiMe2CMe3) and III.

REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 44 OF 76 HCAPLUS COPYRIGHT 2004 ACS on STN

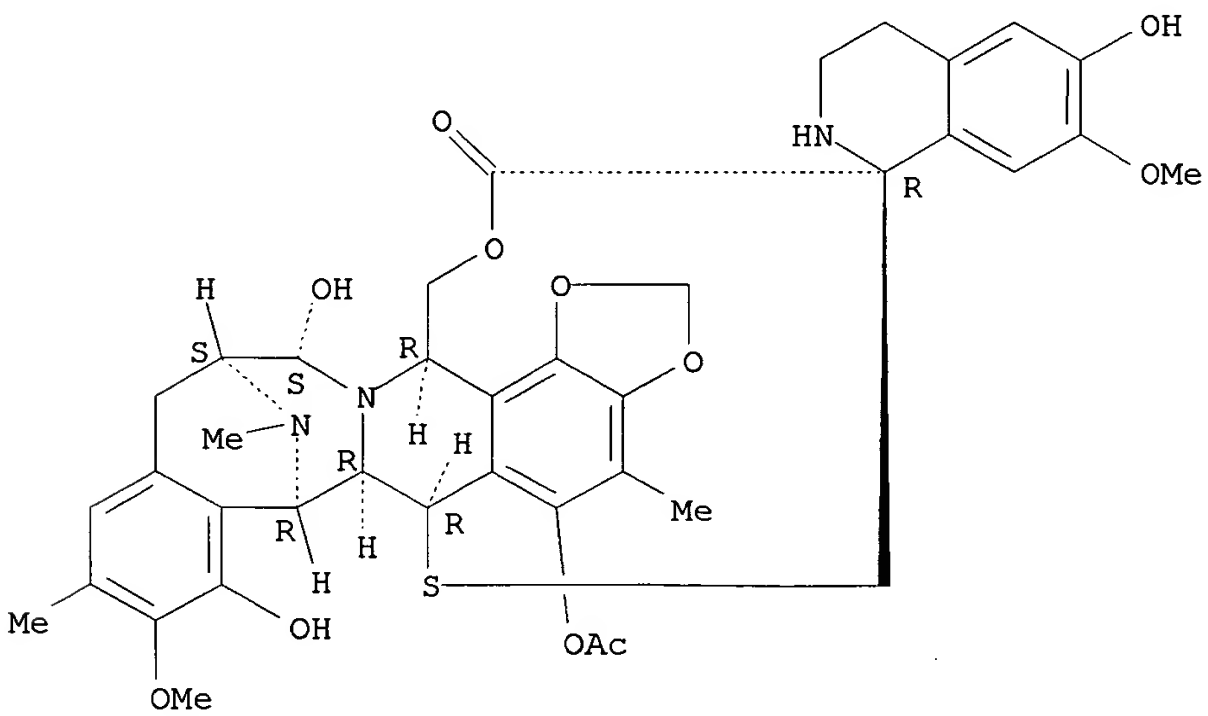
ACCESSION NUMBER: 2000:51188 HCAPLUS
DOCUMENT NUMBER: 132:102290
TITLE: Antitumor compounds from tunicates
AUTHOR(S): Rinehart, Kenneth L.
CORPORATE SOURCE: Department of Chemistry, 454 Roger Adams Laboratory, University of Illinois, Urbana, IL, 61801, USA
SOURCE: Medicinal Research Reviews (**2000**), 20(1), 1-27
CODEN: MRREDD; ISSN: 0198-6325
PUBLISHER: John Wiley & Sons, Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

IT **114899-77-3**, Ecteinascidin 743
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(use of antitumor compds. from tunicates in humans)

RN 114899-77-3 HCAPLUS

CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



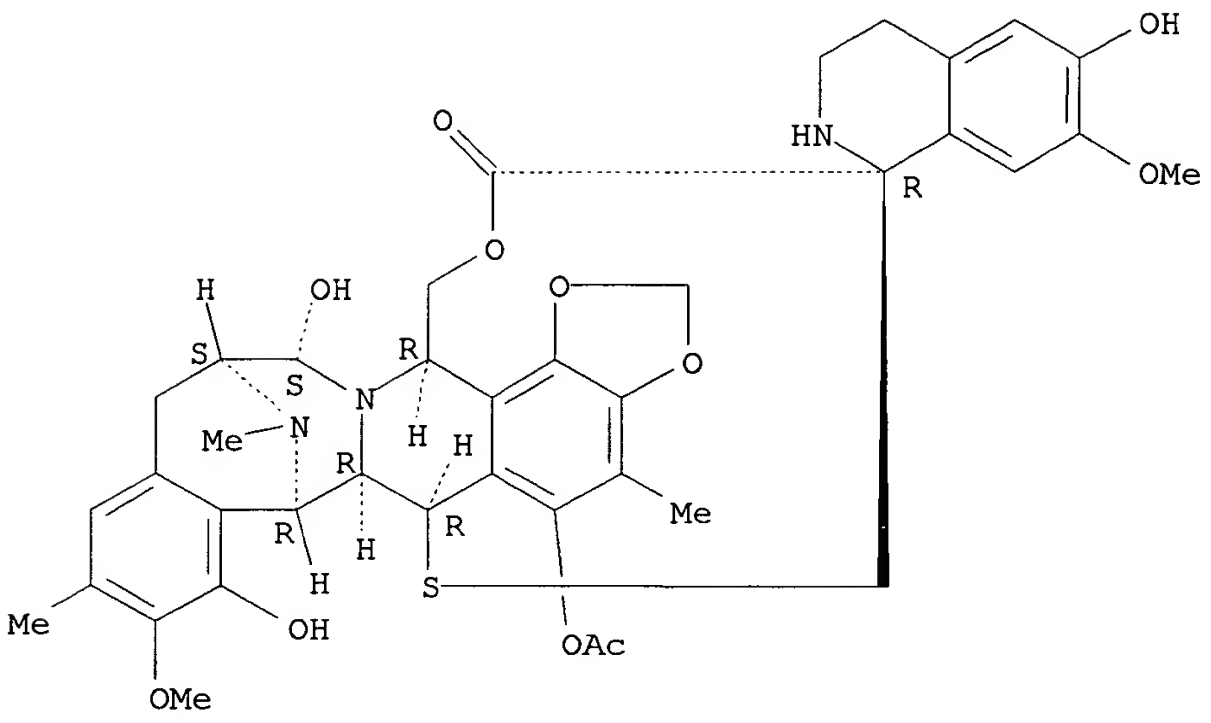
AB A review with 15 refs. Of the six marine-derived compds. that have reached clin. trials as antitumor agents three-didemnin B, Aplidine, and

ecteinascidin 743-are derived from tunicates. Didemnin B (DB), a cyclic depsipeptide from the compound tunicate Tridemnum solidum, was the first marine-derived compound to enter Phases I and II clin. trials. The Phase II studies, sponsored by the U.S. National Cancer Institute, indicated complete or partial remissions with non-Hodgkins lymphoma, but cardiotoxicity caused didemnin B to be dropped from further study. The closely related dehydrodidemnin B (DDB, Aplidine) was isolated in 1988 from a second colonial tunicate, Aplidium albicans, and spectroscopic studies assigned a structural formula in which a pyruvyl group in DDB replaced the lactyl group in DB and syntheses of DDB have been achieved. Aplidine is more active than DB and lacks DB's cardiotoxicity. It was introduced by PharmaMar into Phase I clin. trials in Jan. 1999. The second family of tunicate-derived antitumor agents are the ecteinascidins (ETs), from the mangrove tunicate Ecteinascidia turbinata. The antitumor exts. of E. turbinata were first described in 1969, but the small amount of ETs in E. turbinata prevented their isolation for over a decade. The structures of ETs have been assigned mainly by spectroscopy. Phase II clin. trials with ET 743 are underway. Future supplies of ET's should be available from aquaculture or synthesis.

REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 45 OF 76 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:646322 HCAPLUS
DOCUMENT NUMBER: 132:152010
TITLE: Synthetic study on ecteinascidin 743 starting from D-glucose. [Erratum to document cited in CA131:243449]
AUTHOR(S): Endo, Atsushi; Kan, Toshiyuki; Fukuyama, Tohru
CORPORATE SOURCE: graduate School Pharmaceutical Sciences, CREST, Japan Science Technology Corporation, Univ. Tokyo, Tokyo, 113, Japan
SOURCE: Synlett (**1999**), (10), 1680
CODEN: SYNLES; ISSN: 0936-5214
PUBLISHER: Georg Thieme Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **114899-77-3P**, Ecteinascidin 743
RL: PNU (Preparation, unclassified); PREP (Preparation)
(asym. synthesis of precursor (Erratum))
RN 114899-77-3 HCAPLUS
CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (9CI) (CA INDEX NAME)

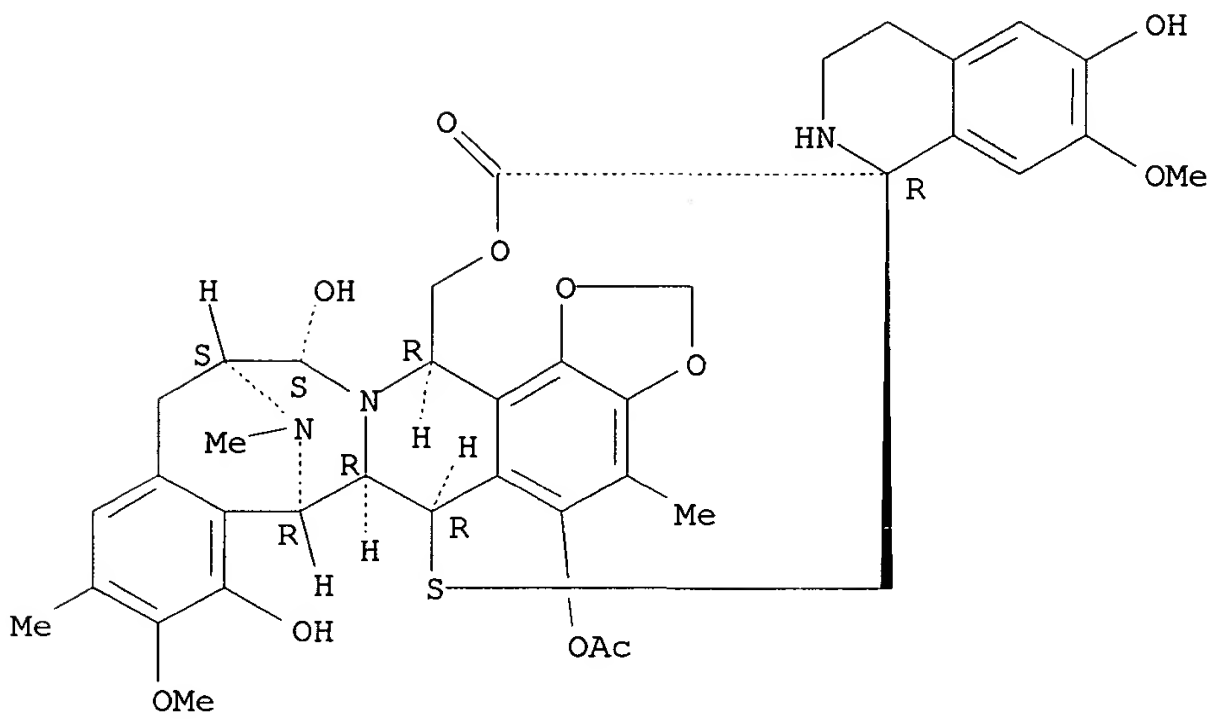
Absolute stereochemistry. Rotation (-).



AB Toshiyuki Kan was incorrectly written as Toshiyuki Kann, and has been corrected

L27 ANSWER 46 OF 76 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:625555 HCAPLUS
DOCUMENT NUMBER: 131:317437
TITLE: Effect of ecteinascidin-743 on the interaction between DNA binding proteins and DNA
AUTHOR(S): Bonfanti, Marina; La Valle, Elisa; Faro, Jose-Maria Fernandez Sousa; Faircloth, Glynn; Caretti, Giuseppina; Mantovani, Roberto; D'Incalci, Maurizio
CORPORATE SOURCE: Department of Oncology, Istituto di Ricerche Farmacologiche Mario Negri, Milan, 20157, Italy
SOURCE: Anti-Cancer Drug Design (**1999**), 14(3), 179-186
CODEN: ACDDEA; ISSN: 0266-9536
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **114899-77-3**, Ecteinascidin-743
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effect of ecteinascidin-743 on interaction between DNA binding proteins and DNA)
RN 114899-77-3 HCAPLUS
CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



AB Ecteinascidin-743 (ET-743) is a tetrahydroisoquinoline alkaloid isolated from Ecteinascidia turbinata, a tunicate growing in mangrove roots in Caribbean. It has been shown to bind in the minor groove of DNA forming covalent adducts by reaction of the N2 of guanine with the carbinolamine moiety. We investigated ET-743 ability to inhibit the binding of different transcription factors to their consensus sequences by using gel shift assays. We have selected three types of factors: (i) oncogene products such as MYC, c-MYB and Maf; (ii) transcriptional activators regulated during the cell cycle as E2F and SRF; and (iii) general transcription factors such as TATA binding protein (TBP), Sp1 and NF-Y. We observed no inhibition of the binding of Sp1, Maf, MYB and MYC. Inhibition of DNA binding was observed for TBP, E2F, SRF at ET-743 concns. ranging from 50 to 300 μM. The inhibition of binding of NF-Y occurs at even lower concns. (i.e. 10-30 μM) when the recombinant subunits of NF-Y are preincubated with the drug, indicating that the inhibition of NF-Y binding does not require previous ET-743 DNA binding. Since NF-Y is a trimer containing two subunits with high resemblance to histones H2B and H2A, we have investigated the effect of ET-743 on nucleosome reconstitution. ET-743 caused a decrease of the nucleosomal band at 100 nM, with the complete disappearance of the band at 3-10 μM. These data suggest that the mode of action of this novel anticancer drug is related to its ability to modify the interaction between some DNA binding proteins and DNA.

REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 47 OF 76 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:507869 HCAPLUS
DOCUMENT NUMBER: 131:252219
TITLE: Poisoning of human DNA topoisomerase I by ecteinascidin 743, an anticancer drug that selectively alkylates DNA in the minor groove
AUTHOR(S): Takebayashi, Yuji; Pourquier, Philippe; Yoshida, Akira; Kohlhagen, Glenda; Pommier, Yves
CORPORATE SOURCE: Laboratory of Molecular Pharmacology, Division of Basic Sciences, National Cancer Institute, National

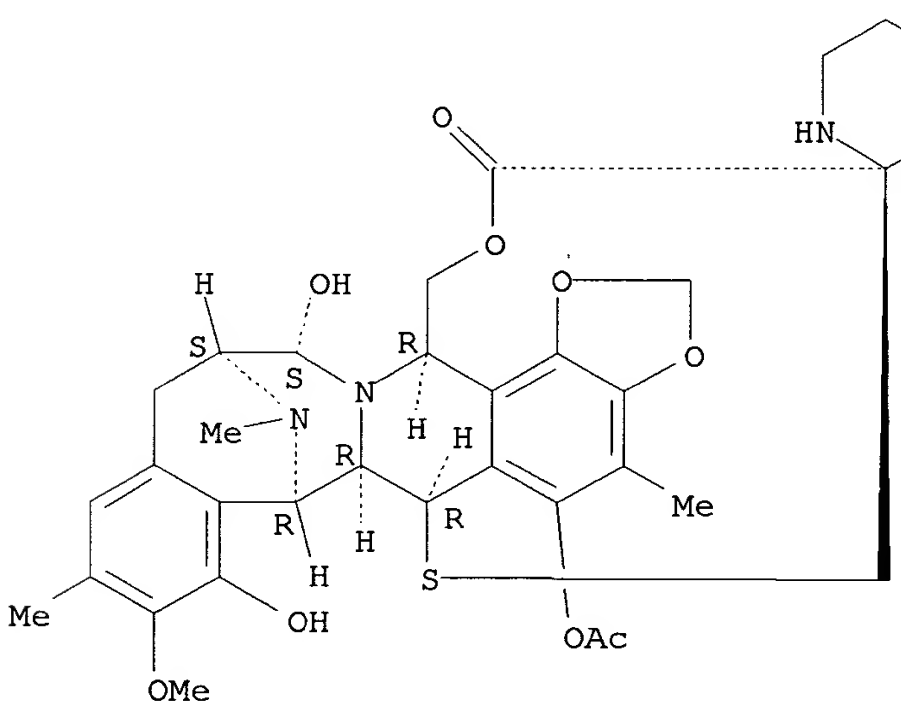
Institutes of Health, Bethesda, MD, 20892-4255, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (**1999**), 96(13), 7196-7201
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **114899-77-3**, Ecteinascidin 743
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(poisoning of human DNA topoisomerase I by ecteinascidin 743)

RN 114899-77-3 HCAPLUS

CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



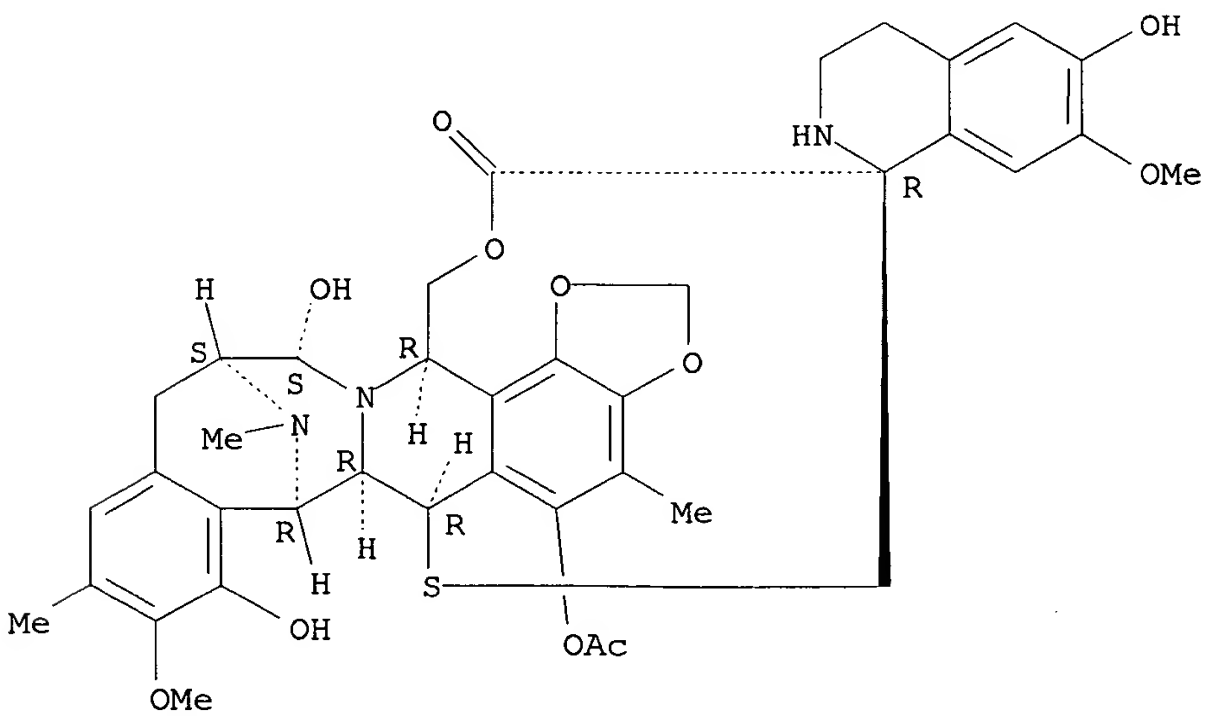
AB Ecteinascidin 743 (Et743, National Service Center 648766) is a potent antitumor agent from the Caribbean tunicate Ecteinascidia turbinata. Although Et743 is presently in clin. trials for human cancers, the mechanisms of antitumor activity of Et743 have not been elucidated. Et743 can alkylate selectively guanine N2 from the DNA minor groove, and this alkylation is reversed by DNA denaturation. Thus, Et743 differs from other DNA alkylating agents presently in the clinic (by both its biochem. activities and its profile of antitumor activity in preclin. models). In this study, we investigated cellular proteins that can bind to DNA alkylated by Et743. By using an oligonucleotide containing high-affinity Et743 binding sites and nuclear exts. from human leukemia CEM cells, we purified a 100-kDa protein as a cellular target of Et743 and identified it as topoisomerase I (top1). Purified top1 was then tested and found to produce cleavage complexes in the presence of Et743, whereas topoisomerase II had no effect. DNA alkylation was essential for the formation of

top1-mediated cleavage complexes by Et743, and the distribution of the drug-induced top1 sites was different for Et743 and camptothecin. Top1-DNA complexes were also detected in Et743-treated CEM cells by using cesium chloride gradient centrifugation followed by top1 immunoblotting. These data indicate that DNA minor groove alkylation by Et743 induces top1-mediated protein-linked DNA breaks and that top1 is a target for Et743 in vitro and in vivo.

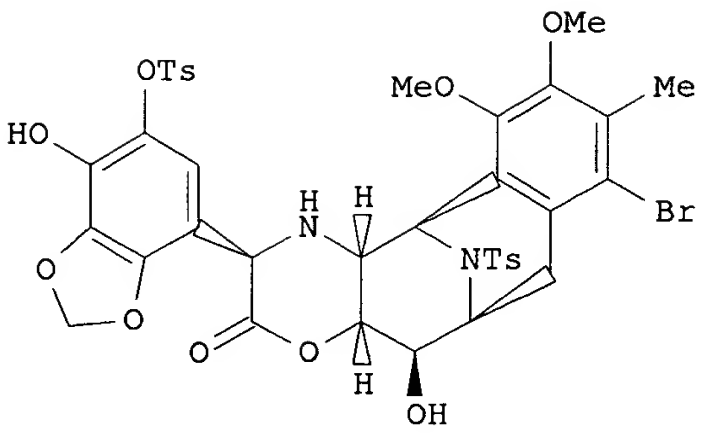
REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 48 OF 76 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:444656 HCAPLUS
DOCUMENT NUMBER: 131:243449
TITLE: Synthetic study on ecteinascidin 743 starting from D-glucose
AUTHOR(S): Endo, Atsushi; Kann, Toshiyuki; Fukuyama, Tohru
CORPORATE SOURCE: Graduate School Pharmaceutical Sciences, CREST, Japan Science Technology Corporation, Univ. Tokyo, Tokyo, 113, Japan
SOURCE: Synlett (**1999**), (7), 1103-1105
CODEN: SYNLES; ISSN: 0936-5214
PUBLISHER: Georg Thieme Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 131:243449
IT **114899-77-3P**, Ecteinascidin 743
RL: PNU (Preparation, unclassified); PREP (Preparation)
(asym. synthesis of precursor)
RN 114899-77-3 HCAPLUS
CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



GI



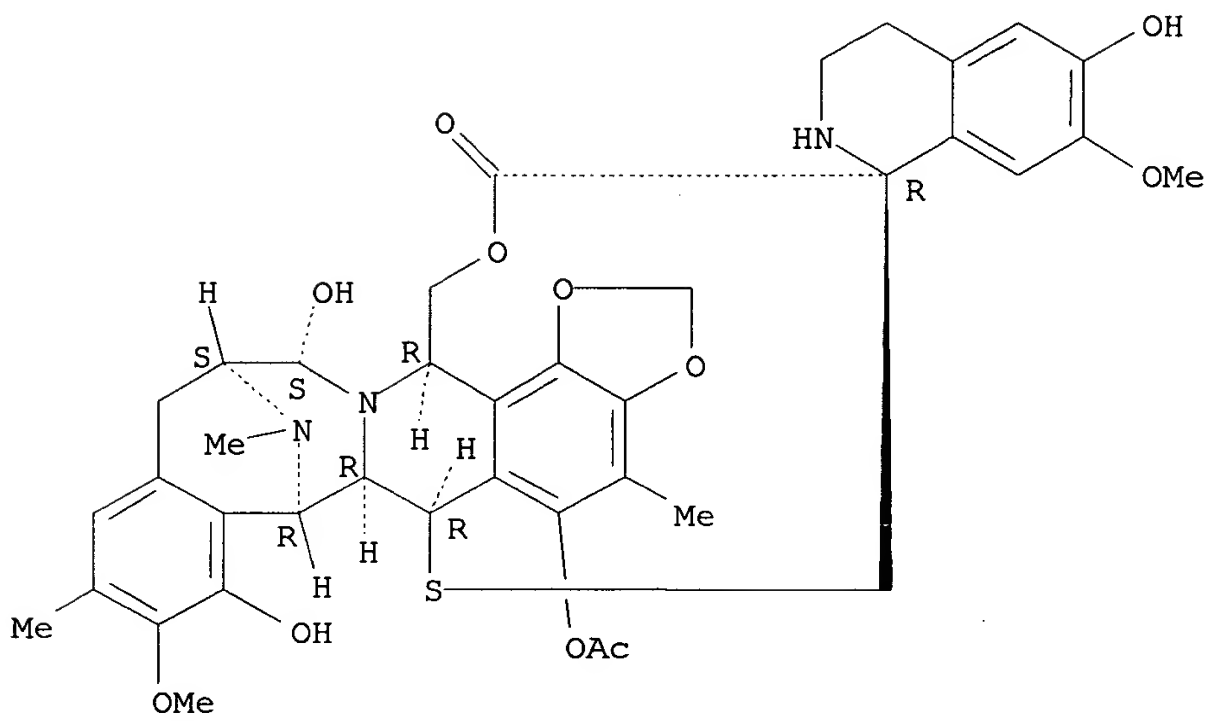
I

AB During the course of synthetic study on ecteinascidin 743, key intermediate I (Ts = 4-MeC6H4SO2) was prepared Stereocontrolled synthesis of I from D-glucose was accomplished using incorporation of 2 N atoms and stereoselective addition of a phenol to an imine as key steps.

REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 49 OF 76 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:395197 HCAPLUS
DOCUMENT NUMBER: 131:193886
TITLE: Ecteinascidin 743: A Minor Groove Alkylator That Bends DNA toward the Major Groove
AUTHOR(S): Zewail-Foote, Maha; Hurley, Laurence H.
CORPORATE SOURCE: Department of Chemistry and Biochemistry and College of Pharmacy Drug Dynamics Institute, The University of Texas at Austin, Austin, TX, 78712, USA
SOURCE: Journal of Medicinal Chemistry (**1999**), 42(14), 2493-2497
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **114899-77-3**, Ecteinascidin 743
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(DNA bending toward major groove in antitumor mechanism of ecteinascidin 743, minor groove alkylator)
RN 114899-77-3 HCAPLUS
CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



AB The ecteinascidins (Ets), which are natural products derived from marine tunicates, exhibit potent antitumor activity. Of the numerous Ets isolated, Et 743 is presently being evaluated in phase II clin. trials. Et 743 binds in the minor groove of DNA and alkylates N2 of guanine. Although structurally similar to saframycin, which exhibits poor activity in cellular assays, Et 743 has shown good efficacy as an antitumor agent. In this study, DNA structural distortions induced by Et 743 were examined to provide insight into the mol. basis for the antitumor activity of Et 743. Electrophoretic mobility shifts of ligated oligomers containing site-directed adducts were used to examine the extent and direction of the Et 743-induced bend. Surprisingly, it was found that Et 743 bends DNA toward the major groove, which is a unique feature among DNA-interactive agents that occupy the minor groove.

REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

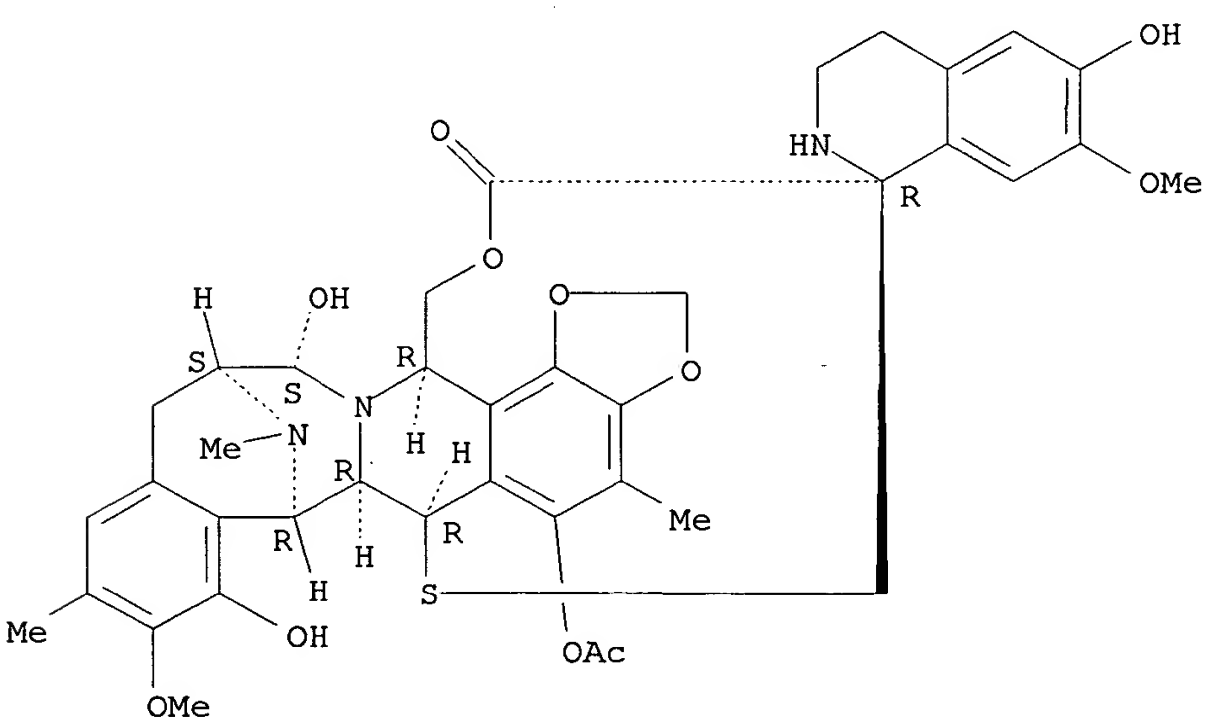
L27 ANSWER 50 OF 76 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:374153 HCAPLUS
DOCUMENT NUMBER: 131:153429
TITLE: Phthalascidin, a synthetic antitumor agent with potency and mode of action comparable to ecteinascidin 743
AUTHOR(S): Martinez, Eduardo J.; Owa, Takashi; Schreiber, Stuart L.; Corey, E. J.
CORPORATE SOURCE: Department of Chemistry and Chemical Biology, Harvard University, Cambridge, MA, 02138, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (**1999**), 96(7), 3496-3501
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **114899-77-3**, Ecteinascidin 743
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)

(phthalascidin as antitumor agent with potency and mode of action comparable to ecteinascidin 743)

RN 114899-77-3 HCAPLUS

CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



AB A series of totally synthetic mols. that are structurally related to the marine natural product ecteinascidin 743 (Et 743) has been prepared and evaluated as antitumor agents. The most active of these, phthalascidin, is very similar to Et 743 with regard to in vitro potency and mode of action across a variety of cell types. The antiproliferative activity of phthalascidin (IC50 = 0.1-1 nM) is greater than that of the agents Taxol, camptothecin, adriamycin, mitomycin C, cisplatin, bleomycin, and etoposide by 1-3 orders of magnitude, and the mechanism of action is clearly different from these currently used drugs. Phthalascidin and Et 743 induce DNA-protein crosslinking and, although they seem to interact with topoisomerase (topo) I (but not topo II), topo I may not be the primary protein target of these agents. Phthalascidin and Et 743 show undiminished potency in camptothecin- and etoposide-resistant cells. Phthalascidin is more readily synthesized and more stable than Et 743, which is currently undergoing clin. trials. The relationship of chemical structure and antitumor activity for this class of mols. has been clarified by this study.

REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 51 OF 76 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1999:322950 HCAPLUS

DOCUMENT NUMBER: 131:157859

TITLE: Enantioselective Synthesis of Saframycin A and Evaluation of Antitumor Activity Relative to Ecteinascidin/Saframycin Hybrids

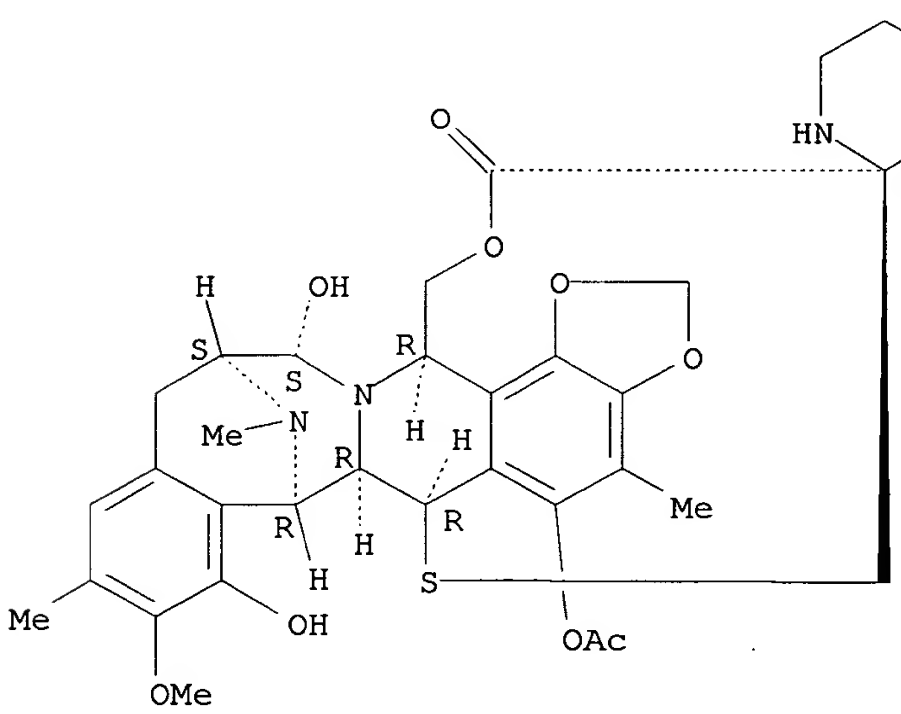
AUTHOR(S): Martinez, Eduardo J.; Corey, E. J.
CORPORATE SOURCE: Department of Chemistry and Chemical Biology, Harvard University, Cambridge, MA, 02138, USA
SOURCE: Organic Letters (**1999**), 1(1), 75-77
CODEN: ORLEF7; ISSN: 1523-7060
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 131:157859

IT **114899-77-3**, Ecteinascidin 743
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(enantioselective synthesis and antitumor activity of saframycin A and relative to ecteinascidin/saframycin hybrids)

RN 114899-77-3 HCAPLUS

CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



GI

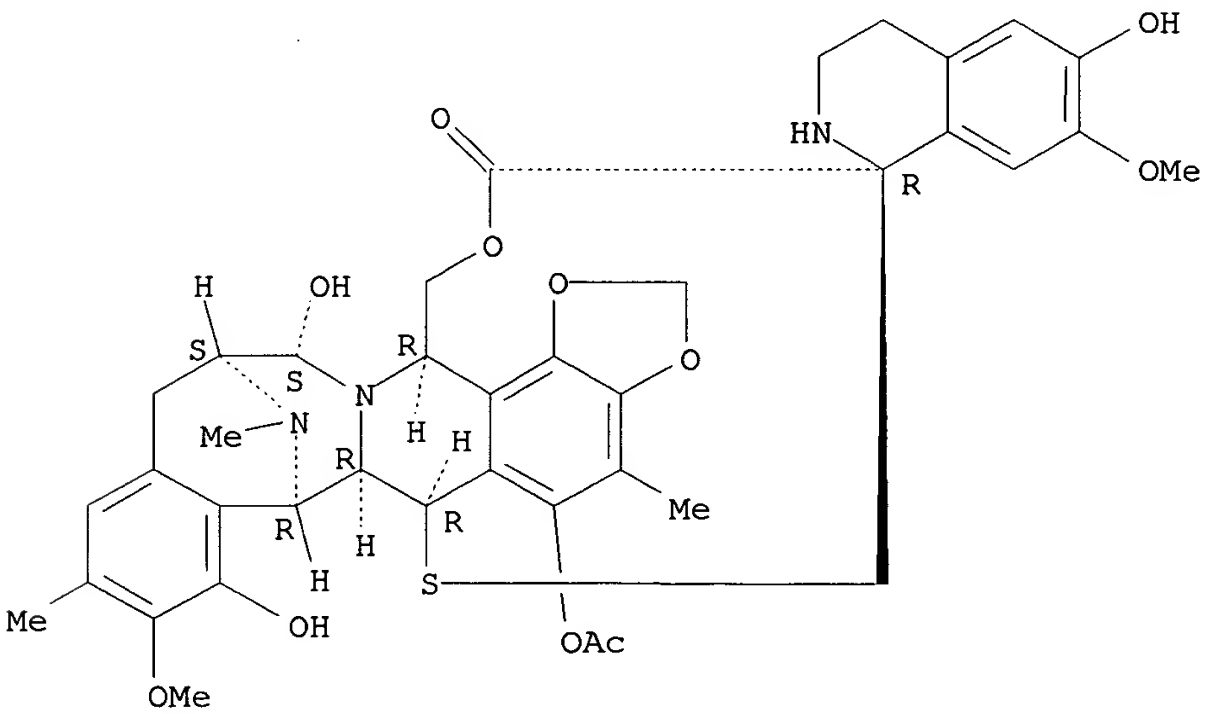
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB A short synthesis of saframycin A (I) is described which begins with the readily available intermediate II (MOM = CH2OMe) previously utilized for the total synthesis of ecteinascidin 743. A key step in this synthesis is the use of 1-fluoro-3,5-dichloropyridinium triflate to oxidize a phenolic ring to a 1,4-benzoquinone unit while simultaneously cleaving a methoxymethyl ether of a different phenolic ring in amide III (MOM = CH2OMe) to the corresponding phenol IV. The common intermediate II for

the synthesis of I and ecteinascidin 743 also allowed the synthesis of two hybrids of these structures. Whole cell bioassays for antitumor activity using lung, colon, melanoma, and prostate-derived tumor cell lines allowed a clear correlation of structure with biol. activity in this series.
REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 52 OF 76 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:267034 HCAPLUS
DOCUMENT NUMBER: 131:96744
TITLE: Pharmacy of the deep - marine organisms as sources of anticancer agents
AUTHOR(S): Jaspars, Marcel
CORPORATE SOURCE: Marine Natural Products Laboratory, Department of Chemistry, Aberdeen University, Aberdeen, AB24 3UE, UK
SOURCE: Advances in Drug Discovery Techniques (**1998**), 65-84. Editor(s): Harvey, Alan L. Wiley: Chichester, UK.
CODEN: 67OWAN
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English
IT **114899-77-3**, Ecteinascidin 743
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(marine organisms as sources of anticancer agents)
RN 114899-77-3 HCAPLUS
CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

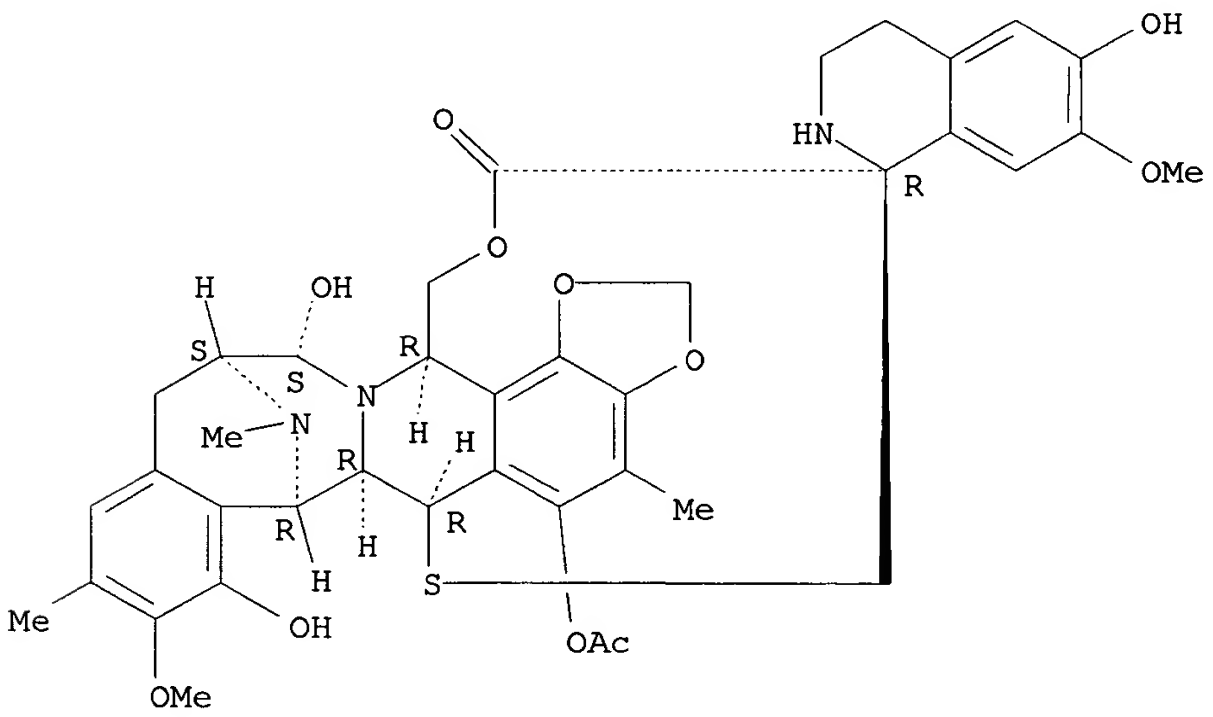


AB A review with about 100 refs. Modes of action and current status in clin. trials of nine natural products from marine organisms (aeroplysinin,

girolline, halichondrin-B, jasplakinolide, didemnin-B, ecteinascidin 743, dolastatin-10, bryostatin-1, and halomon) are described.
REFERENCE COUNT: 89 THERE ARE 89 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 53 OF 76 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:66769 HCAPLUS
DOCUMENT NUMBER: 130:305855
TITLE: Molecular recognition of DNA by ecteinascidin 743
AUTHOR(S): Moore, B. M., II; Seaman, F. C.; Hurley, L. H.
CORPORATE SOURCE: Drug Dynamics Institute, College of Pharmacy, The University of Texas at Austin, Austin, TX, 78712-1074, USA
SOURCE: Ernst Schering Research Foundation Workshop (**1998**), 26(Recent Trends in Molecular Recognition), 81-95
CODEN: ESRWEL; ISSN: 0947-6075
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
IT **114899-77-3**, Ecteinascidin 743
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(mol. recognition of DNA by ecteinascidin 743)
RN 114899-77-3 HCAPLUS
CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



AB A review with 20 refs. Topics covered include preparation, NMR anal. and mol. modeling of the ecteinascidin 743-DNA adduct. A chemical mechanism that gives rise to the alkylation of 6GN2 by ecteinascidin 743 in duplex DNA is

proposed. The results presented not only impact on the development of ecteinascidins but also aid in the de novo design of new DNA-reactive reagents.

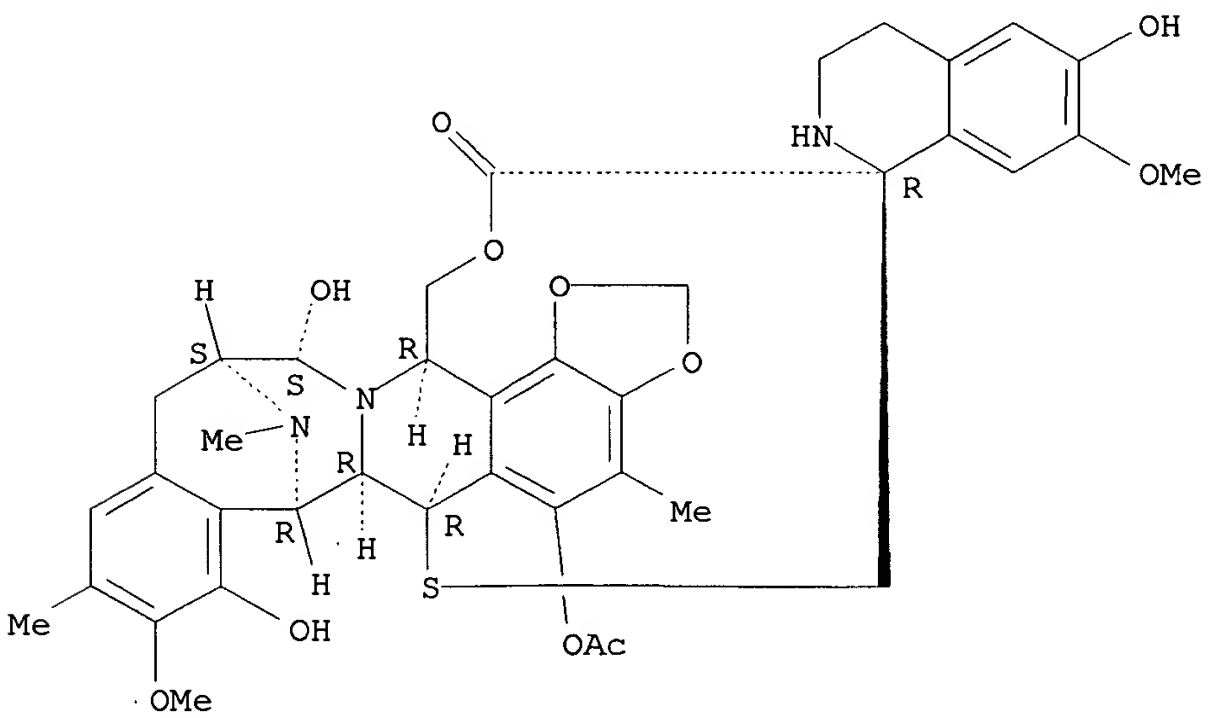
REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 54 OF 76 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:768524 HCAPLUS
DOCUMENT NUMBER: 130:148337
TITLE: Molecular Basis for the DNA Sequence Selectivity of Ecteinascidin 736 and 743: Evidence for the Dominant Role of Direct Readout via Hydrogen Bonding
AUTHOR(S): Seaman, Frederick C.; Hurley, Laurence H.
CORPORATE SOURCE: Drug Dynamics Institute College of Pharmacy, The University of Texas at Austin, Austin, TX, 78712, USA
SOURCE: Journal of the American Chemical Society (**1998**), 120(50), 13028-13041
CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **114899-77-3**, Ecteinascidin 743
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(mol. basis for DNA sequence selectivity of ecteinascidin 736 and 743 and evidence for dominant role of direct readout via hydrogen bonding)

RN 114899-77-3 HCAPLUS
CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



IT **191680-93-0**
RL: FMU (Formation, unclassified); PRP (Properties); FORM (Formation,

nonpreparative)
(mol. basis for DNA sequence selectivity of ecteinascidin 736 and 743 and evidence for dominant role of direct readout via hydrogen bonding)

RN 191680-93-0 HCAPLUS

CN DNA, d(C-G-T-A-A-G-C-T-T-A-C-G), double-stranded complementary, compd. with (6R,6aR,7R,13S,14S,16R,20R)-5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethylspiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one (1:1) (9CI) (CA INDEX NAME)

CM 1

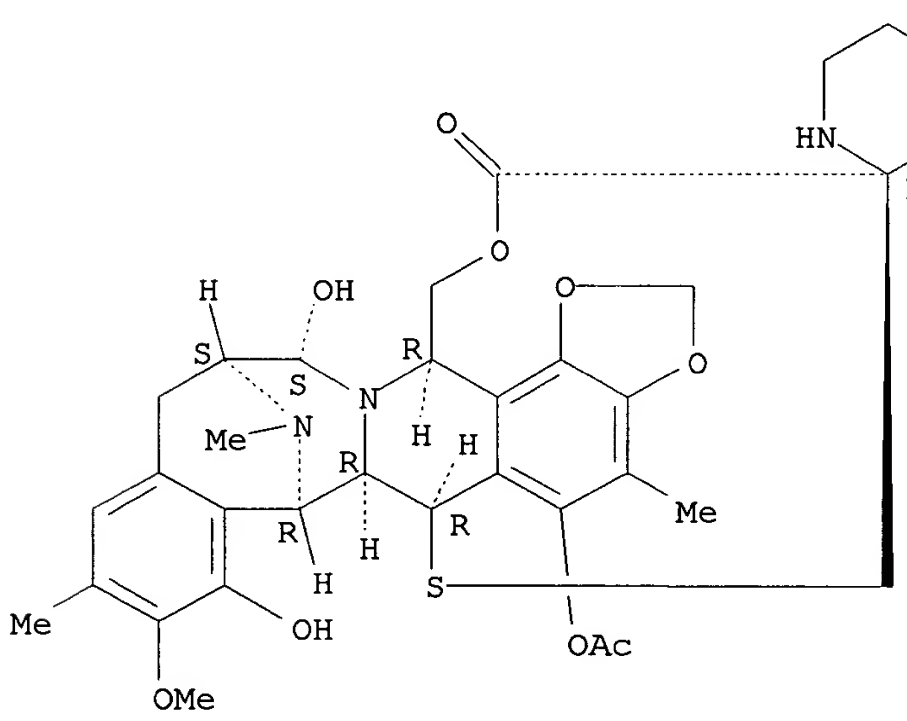
CRN 191235-40-2
CMF Unspecified
CCI MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 114899-77-3
CMF C39 H43 N3 O11 S

Absolute stereochemistry. Rotation (-).



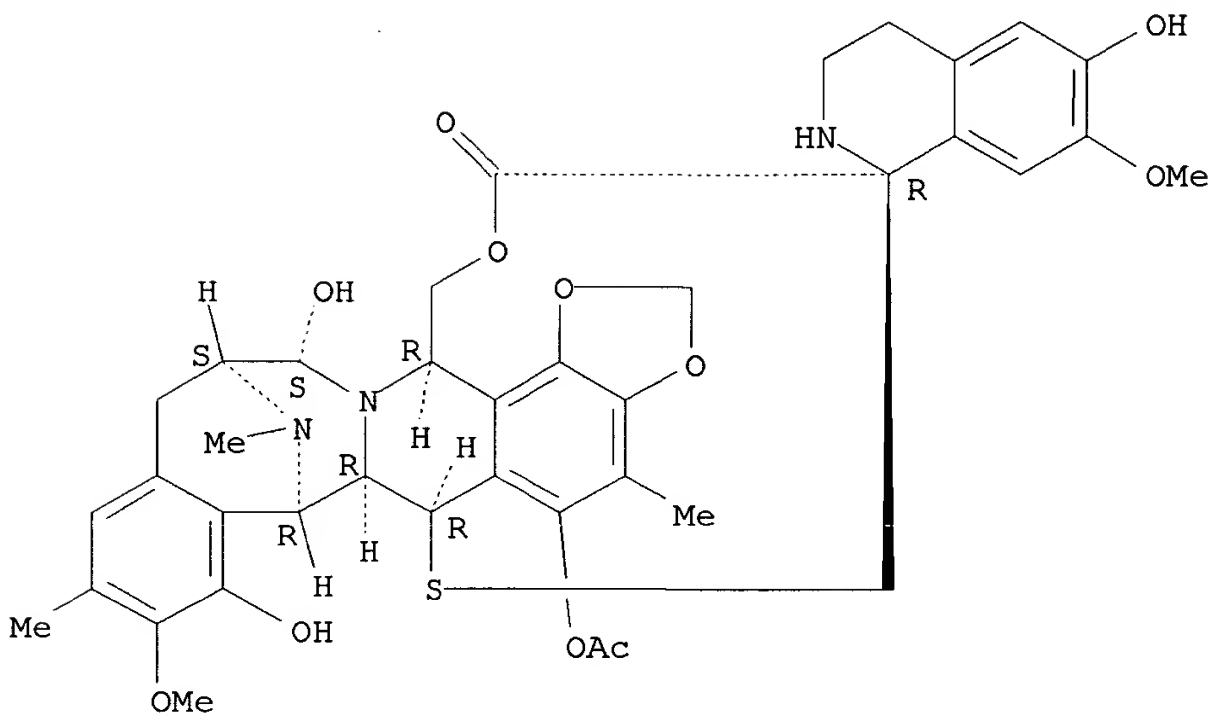
AB The marine natural product ecteinascidin 743 (Et 743) is currently in phase II clin. trials. The authors have undertaken parallel structural and modeling studies of an Et 743-(N2-guanine) 12-mer DNA adduct and an adduct involving the structurally related Et 736 of the same sequence to ascertain the structural basis for the ecteinascidin-DNA sequence selectivity. In contrast to the C-subunit differences found in Et 736 and Et 743, they have identical A-B-subunit scaffolds, which are the principal sites of interaction with DNA bases. These identical scaffolds generate parallel networks of drug-DNA hydrogen bonds that associate the drugs with the three base pairs at the recognition site. The authors propose that these parallel hydrogen bonding networks stabilize the Et 736 and Et 743

A- and B-subunit prealkylation binding complex with the three base pairs and are the major factors governing sequence recognition and reactivity. The possibility that a unique hydrogen-bonding network directs the course of sequence recognition was examined by first characterizing the hydrogen-bonding substituents using 1H NMR properties of the exchangeable protons attached to the hydrogen-bond donor and other protons near the proposed acceptor. Using these exptl. findings as indicators of hydrogen bonding, Et 736-12-mer duplex adduct models (binding and covalent forms) containing the favored sequences 5'-AGC and 5'-CGG were examined by mol. dynamics (MD) to evaluate the stability of the hydrogen bonds in the resulting conformations. The MD-generated models of these favored sequences display optimal donor/acceptor positions for maximizing the number of drug-DNA hydrogen bonds prior to covalent reaction. The results of MD anal. of the carbinolamine (binding) forms of the sequences 5'-GGG (moderately reactive) and 5'-AGT (poorly reactive) suggested reasons for their diminished hydrogen-bonding capability. These exptl. and modeling results provide the structural basis for the following sequence specificity rules: For the target sequence 5'-XGY, the favored base to the 3'-side, Y, is either G or C. When Y is G, then a pyrimidine base (T or C) is favored for X. When Y is C, a purine (A or G) is favored for X.

REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 55 OF 76 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:765472 HCAPLUS
DOCUMENT NUMBER: 129:325669
TITLE: Quantitative determination of Eteinascidin 743 in human plasma by miniaturized high-performance liquid chromatography coupled with electrospray ionization tandem mass spectrometry
AUTHOR(S): Rosing, H.; Hillebrand, M. J. X.; Jimeno, J. M.; Gomez, A.; Floriano, P.; Faircloth, G.; Henrar, R. E. C.; Vermorken, J. B.; Cvitkovic, E.; Bult, A.; Beijnen, J. H.
CORPORATE SOURCE: Department of Pharmacy and Pharmacology, Slotervaart Hospital/The Netherlands Cancer Institute, Amsterdam, 1066 EC, Neth.
SOURCE: Journal of Mass Spectrometry (**1998**), 33(11), 1134-1140
CODEN: JMSPFJ; ISSN: 1076-5174
PUBLISHER: John Wiley & Sons Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **114899-77-3**, Ecteinascidin 743
RL: ANT (Analyte); ANST (Analytical study)
(determination of Ecteinascidin 743 in human plasma by HPLC with electrospray
ionization tandem mass spectrometry)
RN 114899-77-3 HCAPLUS
CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



AB A method was developed for the determination of Ecteinascidin 743 (ET-743) using miniaturized liquid chromatog. (LC) coupled to an electrospray ionization sample inlet (TurbolonSpray) and 2 quadrupole mass analyzers (LC/ESI-MS/MS). Solid-phase extraction was used as a sample pretreatment procedure. Ecteinascidin 743 is a very potent anticancer compound and is administered in μg m-2 dosages, which demands special requirements in terms of sensitivity for the anal. method supporting clin. pharmacokinetic studies. Using conventional LC/UV, a lower limit of quantitation (LLQ) of 1 ng mL-1 plasma was reached using a 500 μL sample volume, but LC/ESI-MS/MS permitted an LLQ of 10 pg mL-1. The latter method was accurate and precise, and provided a broad linear concentration range of 0.010-2.50 ng mL-1.

REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

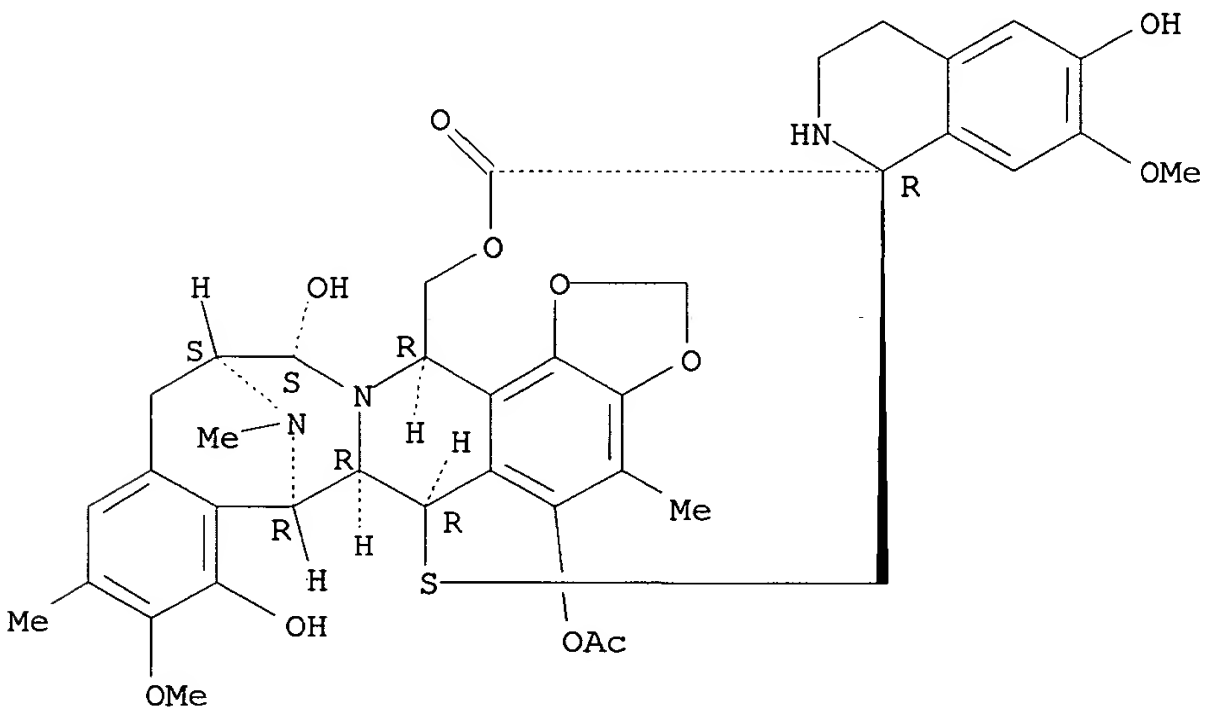
L27 ANSWER 56 OF 76 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:596553 HCAPLUS
DOCUMENT NUMBER: 129:285720
TITLE: Mechanism for the Catalytic Activation of Ecteinascidin 743 and Its Subsequent Alkylation of Guanine N2. [Erratum to document cited in CA128:265809]
AUTHOR(S): Moore, Bob M., II; Seaman, Frederick C.; Wheelhouse, Richard T.; Hurley, Laurence H.
CORPORATE SOURCE: Drug Dynamics Institute College of Pharmacy, University of Texas, Austin, TX, 78712-1074, USA
SOURCE: Journal of the American Chemical Society (**1998**), 120(38), 9975
CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **114899-77-3**, Ecteinascidin 743
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL

(Biological study); USES (Uses)
(mechanism for catalytic activation of ecteinascidin 743 and its subsequent alkylation of guanine N2 (Erratum))

RN 114899-77-3 HCAPLUS

CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



AB Three of the structures in Chart 1 were mislabeled in the text: structure 2 is saframycin S, structure 3 is naphthyridinomycin, and structure 4 is anthramycin.

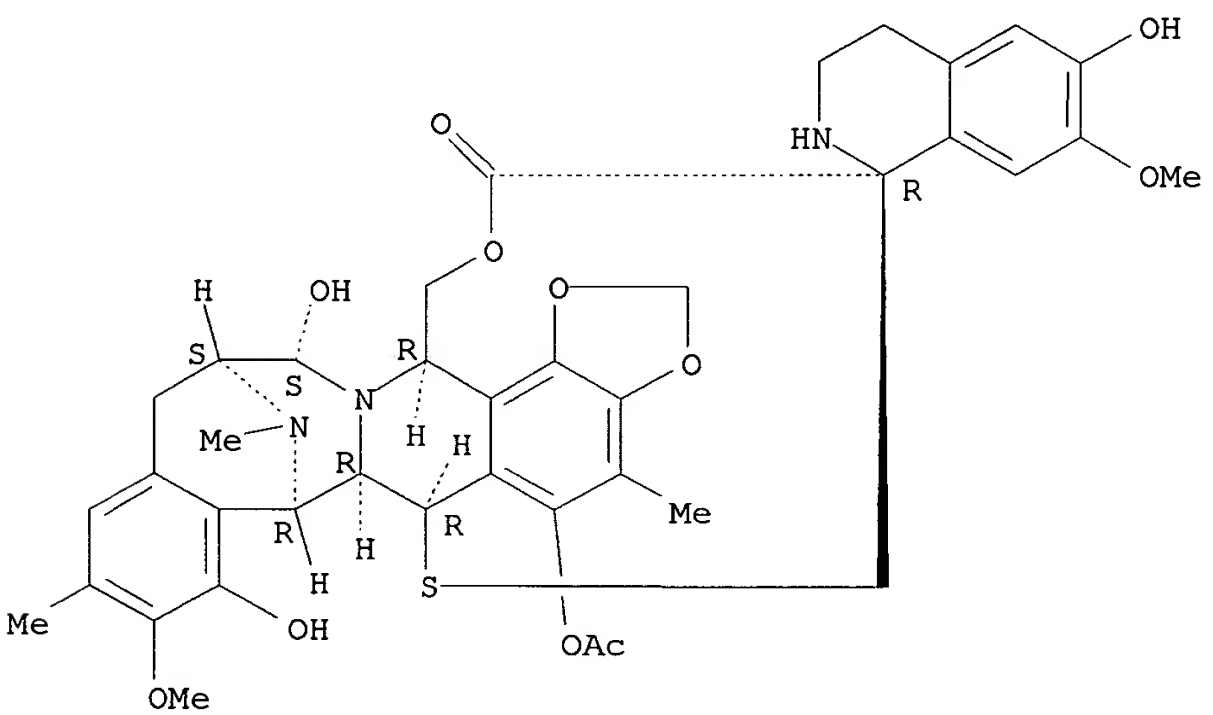
L27 ANSWER 57 OF 76 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:565299 HCAPLUS
DOCUMENT NUMBER: 129:270190
TITLE: Ecteinascidin-743, a new marine natural product with potent antitumor activity on human ovarian carcinoma xenografts
AUTHOR(S): Valoti, Giorgio; Nicoletti, M. Ines; Pellegrino, Antonio; Jimeno, Jose; Hendriks, Hans; D'Incalci, Maurizio; Faircloth, Glynn; Giavazzi, Raffaella
CORPORATE SOURCE: Mario Negri Institute for Pharmacological Research, Bergamo, Italy
SOURCE: Clinical Cancer Research (**1998**), 4(8), 1977-1983
CODEN: CCREF4; ISSN: 1078-0432
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **114899-77-3**, Ecteinascidin743
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); OCCU (Occurrence); USES (Uses)

(ET-743; ecteinascidin-743, a new marine natural product with potent antitumor activity on human ovarian carcinoma xenografts)

RN 114899-77-3 HCAPLUS

CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

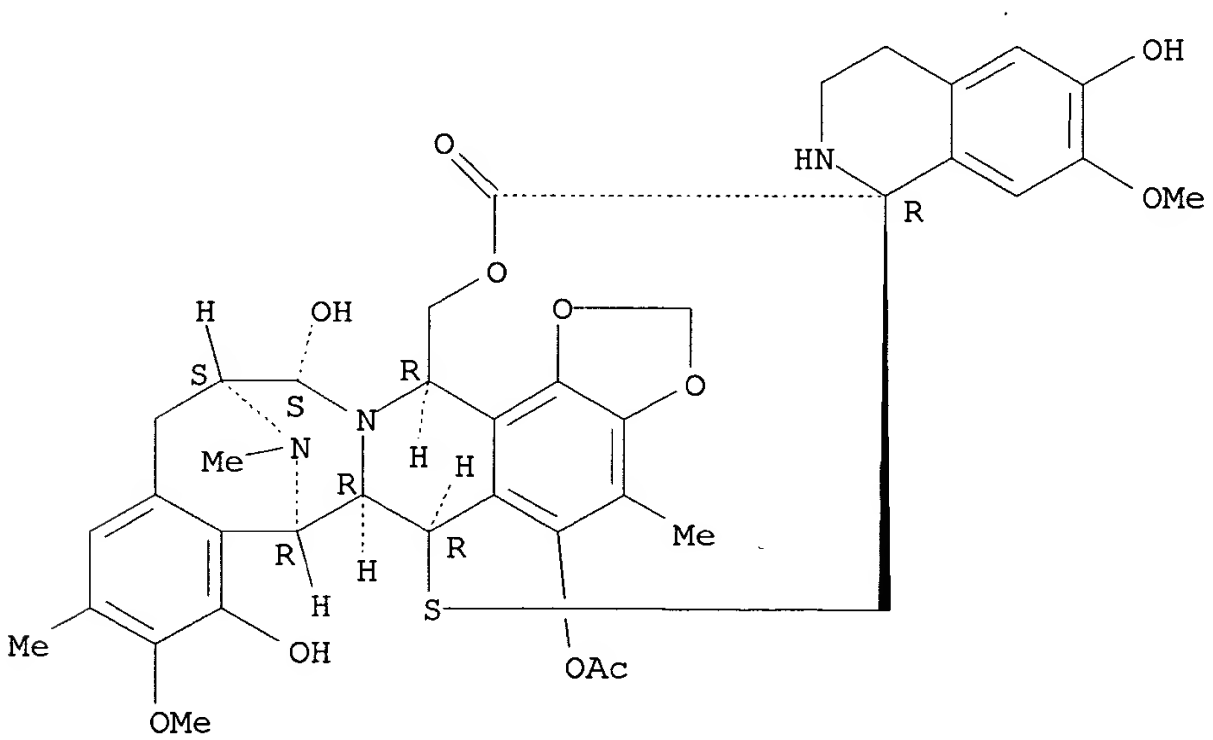


AB The antitumor activity of ecteinascidin (ET)-743, a novel marine natural product, was evaluated against a panel of human ovarian carcinoma xenografts characterized by different malignant behaviors and drug responsiveness in nude mice. These tumor models included three xenografts transplanted s.c. (HOC18, HOC22-S, and MNB-PTX-1) into nude mice, representing different levels of sensitivity to cisplatinum (DDP), which was used as reference drug for ovarian carcinoma, and two other xenografts (HOC22 and HOC8), which are highly malignant in the peritoneal cavity of nude mice, representing the growth pattern of this neoplasm. At the maximum tolerated dose of 0.2 mg/kg using an intermittent schedule of one i.v. injection every 4 days, ET-743 was highly active against HOC22-S (sensitive to DDP), inducing long-lasting, complete regressions, and against HOC18 (marginally sensitive to DDP), inducing partial tumor regressions. Moreover, significant growth delay was observed in mice bearing late-stage HOC18 tumor (400-mg tumor weight; nonresponsive to DDP). ET-743, however, was not active against MNB-PTX-1, a tumor that is highly resistant to chemotherapy, including DDP. In the i.p. ovarian carcinoma xenograft model, ET-743 at the maximum tolerated dose induced complete tumor remissions in all mice bearing HOC22 tumor, with 25% histopathol. confirmed cures, and produced marginal tumor growth delay against HOC8. These results indicate that ET-743 is a potent drug against ovarian carcinoma xenografts, being equally as active or more efficacious than DDP in the same tumor line. Our findings with human ovarian carcinoma xenografts justify clin. assessment of this drug with this tumor target.

REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 58 OF 76 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:467222 HCAPLUS
DOCUMENT NUMBER: 129:211157
TITLE: Analysis of Ecteinascidin 743, a new potent marine-derived anticancer drug, in human plasma by high-performance liquid chromatography in combination with solid-phase extraction
AUTHOR(S): Rosing, H.; Hillebrand, M. J. X.; Jimeno, J. M.; Gomez, A.; Floriano, P.; Faircloth, G.; Cameron, L.; Henrar, R. E. C.; Vermorken, J. B.; Bult, A.; Beijnen, J. H.
CORPORATE SOURCE: Dept. of Pharmacy and Pharmacology, Slotervaart Hospital/Netherlands Cancer Institute, Louwesweg 6, Amsterdam, 1066 EC, Neth.
SOURCE: Journal of Chromatography, B: Biomedical Sciences and Applications (**1998**), 710(1 + 2), 183-189
CODEN: JCBBEP; ISSN: 0378-4347
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **114899-77-3**, Ecteinascidin 743
RL: ANT (Analyte); BPR (Biological process); BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study); PROC (Process)
(determination of anticancer drug Ecteinascidin 743 in human plasma by HPLC in
combination with solid-phase extraction)
RN 114899-77-3 HCAPLUS
CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



AB A reversed-phase high-performance liquid chromatog. method has been developed and validated for the quantification of the novel anticancer drug Ecteinascidin 743 in human plasma. The sample pretreatment of the plasma samples involved a solid-phase extraction (SPE) on cyano columns. Propyl-p-hydroxybenzoate was added after the sample pretreatment to correct for variability in injection vols. The separation was performed on a Zorbax SB-C18 column (75+4.6 mm I.D., particle size 3.5 μm) with acetonitrile-25 mM phosphate buffer, pH 5.0 (70:30, volume/volume) as the mobile phase. The flow-rate was 1.0 mL/min and the eluent was monitored at 210 nm. The accuracies and precisions of the assay fall within ±15% for all quality control samples and within ±20% for the lower limit of quantitation, which was 1.0 ng/mL using 500 μl of plasma. The overall recovery of the sample pretreatment procedure for Ecteinascidin 743 was 87.0±5.9%. The drug was found to be stable in human plasma at -30°C for at least 2 mo. At room temperature Ecteinascidin 743 was stable in human plasma for 5 h at most.

REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 59 OF 76 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1998:146723 HCAPLUS
DOCUMENT NUMBER: 128:205023
TITLE: Process for the synthesis of ecteinascidins
INVENTOR(S): Corey, Elias J.; Gin, David
PATENT ASSIGNEE(S): President and Fellows of Harvard College, USA
SOURCE: U.S., 55 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
US 5721362	A	19980224	US 1996-715541	19960918	<--
WO 9812198	A1	19980326	WO 1997-US16470	19970917	<--
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG					
AU 9744205	A1	19980414	AU 1997-44205	19970917	<--
AU 738282	B2	20010913			
EP 931083	A1	19990728	EP 1997-942526	19970917	<--
EP 931083	B1	20030219			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO					
CN 1237974	A	19991208	CN 1997-199846	19970917	<--
CN 1096463	B	20021218			
NZ 334704	A	20000929	NZ 1997-334704	19970917	<--
JP 2001501196	T2	20010130	JP 1998-514837	19970917	<--
BR 9712073	A	20020115	BR 1997-12073	19970917	
RU 2194709	C2	20021220	RU 1999-105564	19970917	
AT 232868	E	20030315	AT 1997-942526	19970917	
PT 931083	T	20030731	PT 1997-97942526	19970917	

NO 9901301	A	19990514	NO 1999-1301	19990317	<--
MX 9902576	A	20000228	MX 1999-2576	19990317	<--
KR 2000036242	A	20000626	KR 1999-702328	19990318	<--

PRIORITY APPLN. INFO.: US 1996-715541 A 19960918
WO 1997-US16470 W 19970917

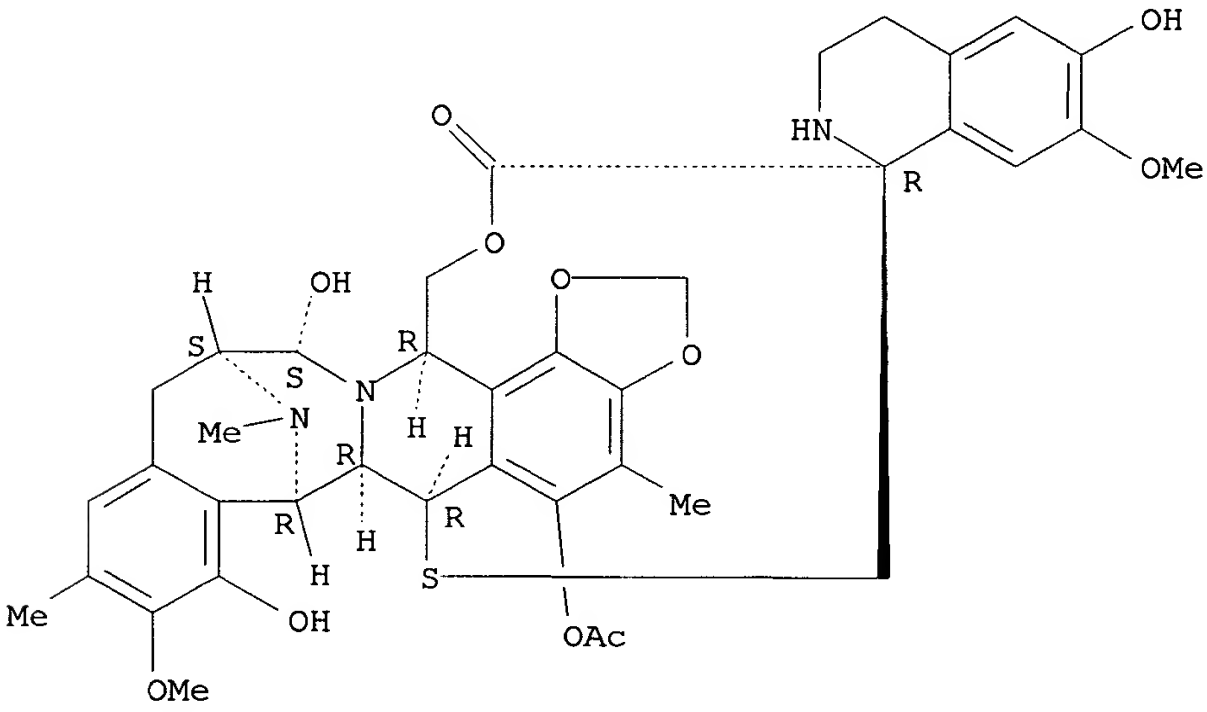
OTHER SOURCE(S): MARPAT 128:205023

IT **114899-77-3P**, Ecteinascidin 743
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(synthesis of marine derived antitumor agent ecteinascidin 743)

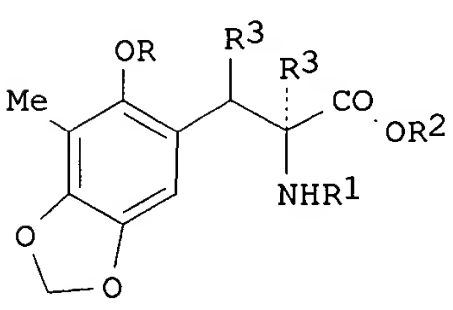
RN 114899-77-3 HCAPLUS

CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (9CI) (CA INDEX NAME)

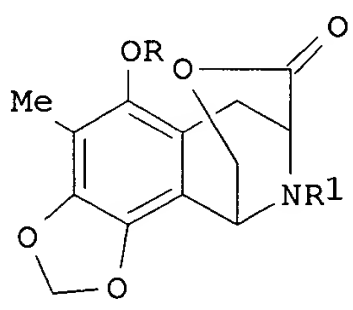
Absolute stereochemistry. Rotation (-).



GI



I



II

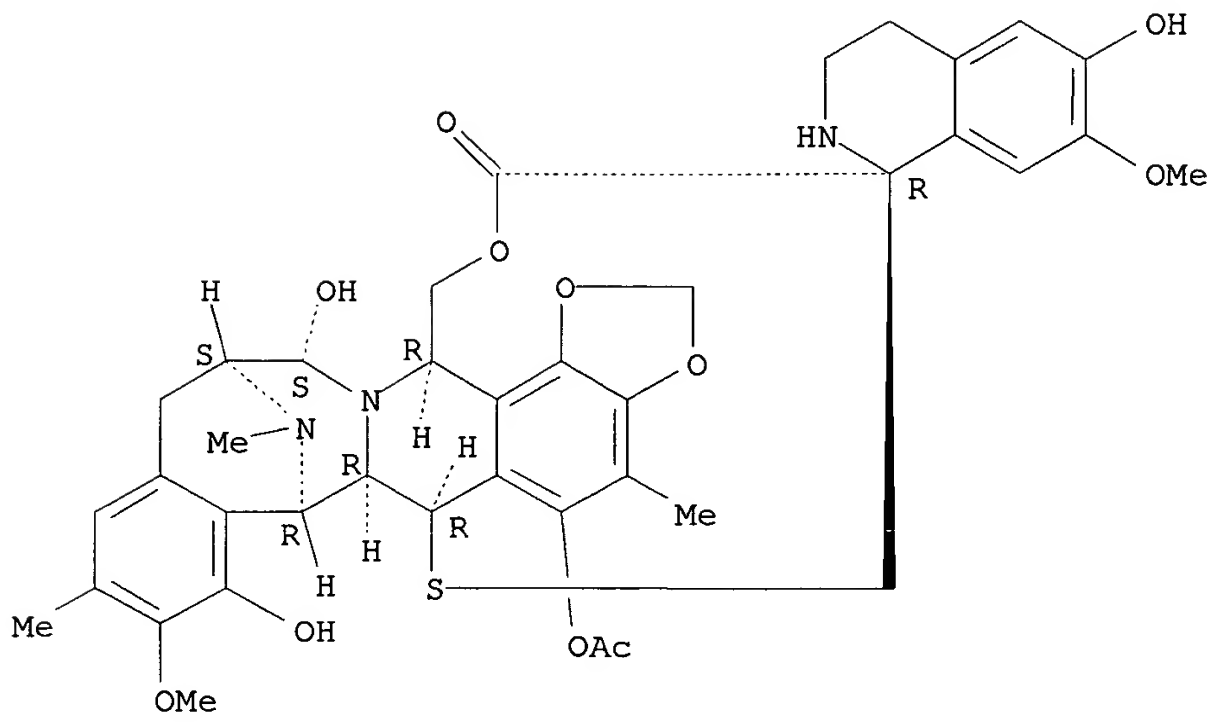
AB An enantiocontrolled convergent synthetic route for the preparation of ecteinascidin 743, an exceedingly potent and rare marine derived antitumor agent (no data) slated for clin. trials, was described. Thus, (-)-ecteinascidin 743 was prepared in a multistep synthetic sequence which

included Rh[(COD)(R,R)-DIPAMP]+BF4- catalyzed enantioselective hydrogenation of β-unsatd. ester (Z)- I [R = benzyl, R1 = CO2CH2Ph, R2 = CH2CH(OMe)2, R3R3 = bond] to form amino acid acetal ester I [R3 = H] and subsequent intramol. cyclization of the corresponding aldehyde I [R2 = CH2CHO, R3 = H] to form ecteinascidin subunit II.

REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 60 OF 76 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:131548 HCAPLUS
DOCUMENT NUMBER: 128:265809
TITLE: Mechanism for the Catalytic Activation of Ecteinascidin 743 and Its Subsequent Alkylation of Guanine N2
AUTHOR(S): Moore, Bob M., II; Seaman, Frederick C.; Wheelhouse, Richard T.; Hurley, Laurence H.
CORPORATE SOURCE: Drug Dynamics Institute College of Pharmacy, University of Texas, Austin, TX, 78712-1074, USA
SOURCE: Journal of the American Chemical Society (**1998**), 120(10), 2490-2491
CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **114899-77-3**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(mechanism for catalytic activation of ecteinascidin 743 and its subsequent alkylation of guanine N2)
RN 114899-77-3 HCAPLUS
CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



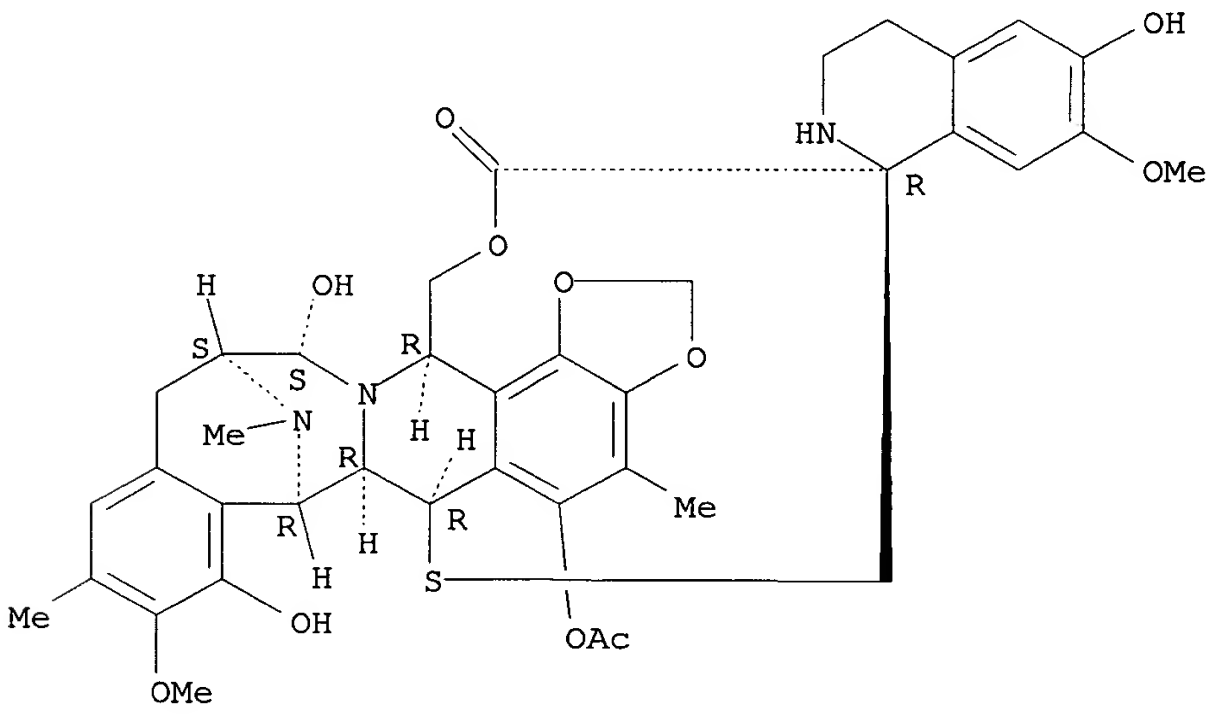
AB Ecteinascidin 743 (Et 743) is the first of a novel class of marine alkaloids to be introduced into phase 1 clin. trials against a variety of solid tumor types. These alkaloids are believed to exert in vivo activity, at least in part, via interactions with duplex DNA. We have previously reported an NMR-based model of Et 743 bound to a 23-mer oligonucleotide; now the protonation state of the drug and DNA in the covalent adduct is reported. Reaction of Et 743 with an isotopically labeled (13C, 15N) and a natural abundance 12-mer oligonucleotide containing an AGC alkylation site yielded a stable GN2-alkylated Et 743-DNA adduct. Two-dimensional NMR spectroscopy (NOESY, COSY, TOCSY) of the natural abundance Et 743-DNA adduct in H2O-D2O (9:1) demonstrated that N12 of Et 743 is the only site of protonation of the drug. The labeled Et 743-DNA adduct was studied using HMBC and HMQC NMR spectroscopy, and the results indicated that the DNA bases were not protonated in the covalent adduct. These data, in combination with earlier results, were employed to propose a specific mechanism for the catalytic activation of the carbinolamine and subsequent alkylation of GN2 by the iminium intermediate. Our mechanism utilizes the proton on 12N of the free Et 743 to activate the carbinolamine for formation of an iminium intermediate. This intermediate alkylates DNA, which is followed by a water mediated proton transfer of one of the GN2H protons back to 12N of Et 743. These data provide information regarding the chemical and structural features of Et 743 that is required for in vivo activity. In general, these results suggest a general mechanism for the catalytic activation of other carbinolamine-containing antibiotics.

REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 61 OF 76 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:96227 HCAPLUS
DOCUMENT NUMBER: 128:192802
TITLE: The first enantioselective total synthesis of dolabellatrienone and ecteinascidin 743
AUTHOR(S): Kania, Robert S.
CORPORATE SOURCE: Harvard Univ., Cambridge, MA, USA
SOURCE: (**1997**) 225 pp. Avail.: UMI, Order No.

DA9810673
From: Diss. Abstr. Int., B 1998, 58(9), 4807
DOCUMENT TYPE: Dissertation
LANGUAGE: English
IT **114899-77-3P**, Ecteinascidin 743
RL: SPN (Synthetic preparation); PREP (Preparation)
(enantioselective total synthesis of dolabellatrienone and ecteinascidin 743)
RN 114899-77-3 HCAPLUS
CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



AB Unavailable

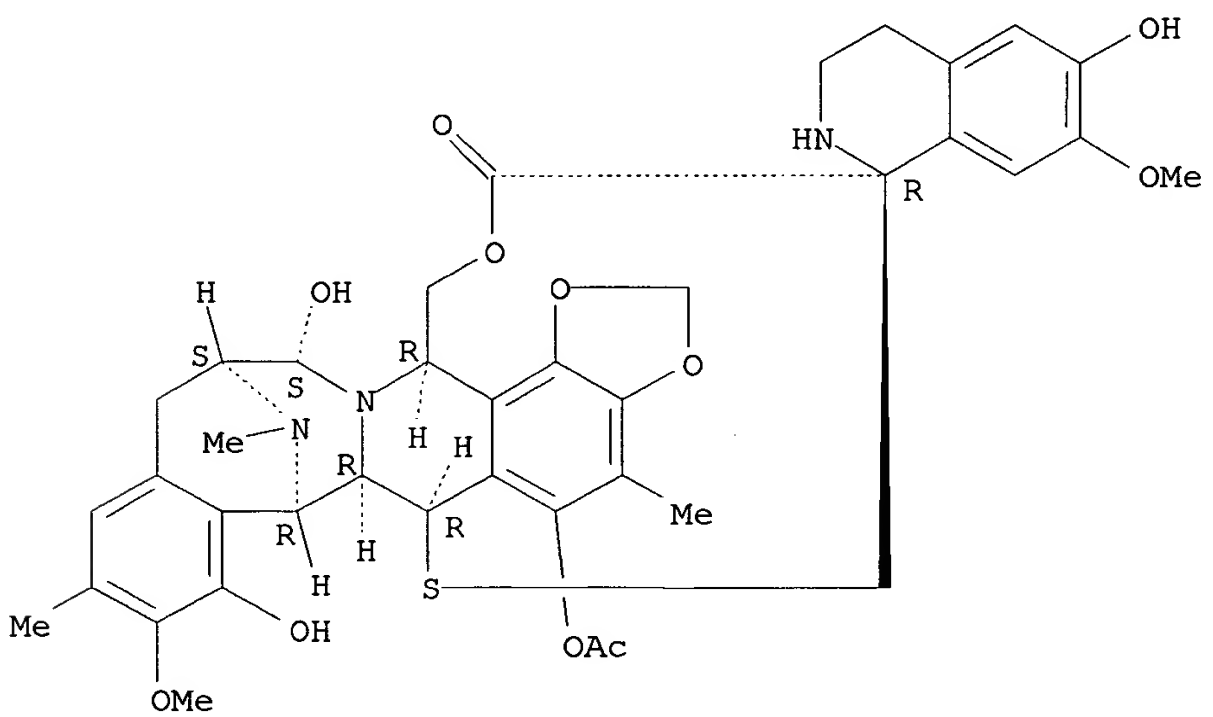
L27 ANSWER 62 OF 76 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:335299 HCAPLUS
DOCUMENT NUMBER: 127:75608
TITLE: NMR-Based Model of an Ecteinascidin 743-DNA Adduct
AUTHOR(S): Moore, Bob M., II; Seaman, Frederick C.; Hurley, Laurence H.
CORPORATE SOURCE: Drug Dynamics Institute, University of Texas, Austin, TX, 78712-1074, USA
SOURCE: Journal of the American Chemical Society (**1997**), 119(23), 5475-5476
CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **114899-77-3**, Ecteinascidin 743
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)

(NMR-based model of ecteinascidin 743-DNA adduct in relation to antitumor activity)

RN 114899-77-3 HCAPLUS

CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



IT **191680-93-0**

RL: FMU (Formation, unclassified); PRP (Properties); FORM (Formation, nonpreparative)

(NMR-based model of ecteinascidin 743-DNA adduct in relation to antitumor activity)

RN 191680-93-0 HCAPLUS

CN DNA, d(C-G-T-A-A-G-C-T-T-A-C-G), double-stranded complementary, compd. with (6R,6aR,7R,13S,14S,16R,20R)-5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethylspiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one (1:1) (9CI) (CA INDEX NAME)

CM 1

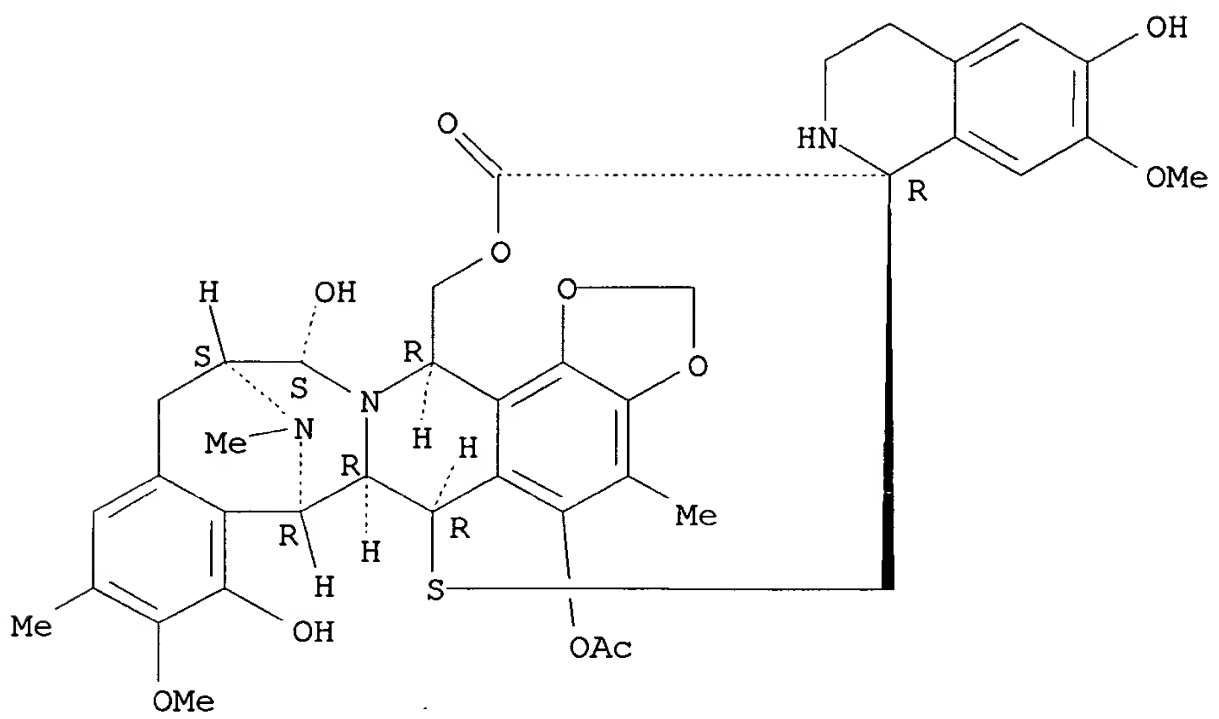
CRN 191235-40-2
CMF Unspecified
CCI MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

CM 2

CRN 114899-77-3
CMF C39 H43 N3 O11 S

Absolute stereochemistry. Rotation (-).

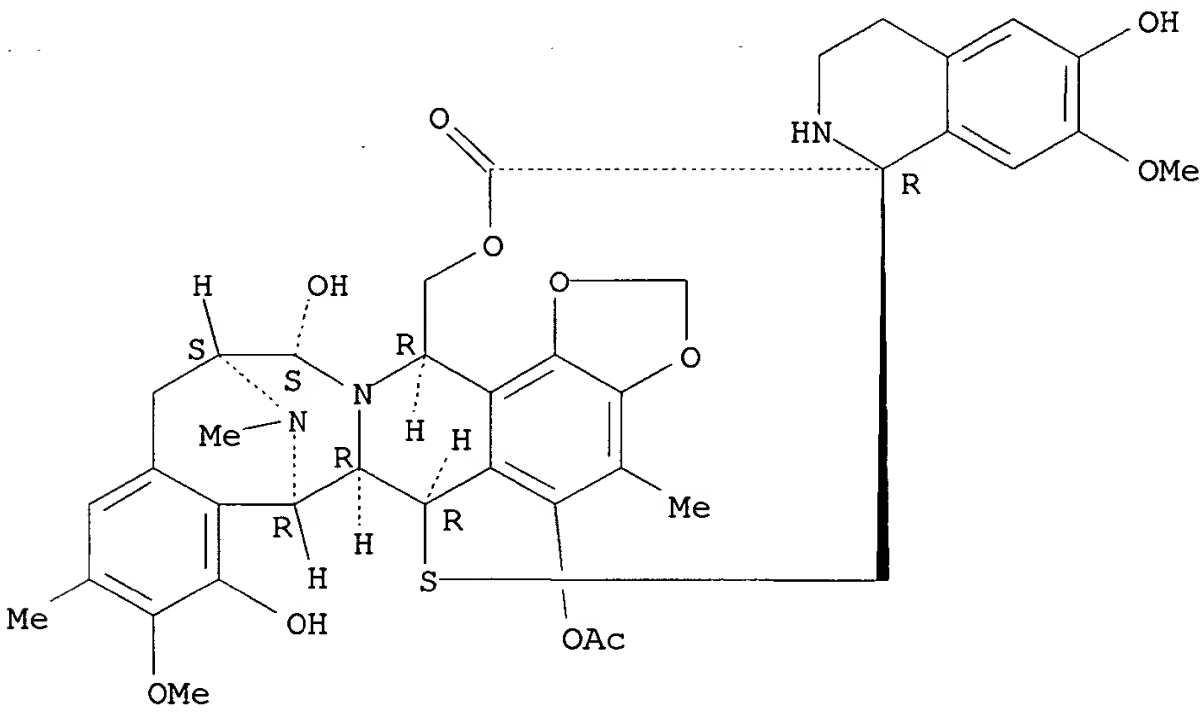


AB Ecteinascidin 743 (Et 743) is an antitumor agent isolated from the Caribbean tunicate Ecteinascidia turbinata. Promising efficacy of Et 743 in several human xenograft models in mice prompted the introduction of this agent into preclin. trials. Evidence suggests that Et 743 exerts its antitumor activity, at least in part, via interactions with DNA; therefore, the authors present a model of Et 743 bound to a 12-mer oligonucleotide based on protein-proton connectivities derived from high-field NMR expts. Reaction of Et 743 with a 12-mer oligonucleotide duplex containing an AGC alkylation site yielded a stable GN2 alkylated oligonucleotide-Et 743 adduct. Interproton connectivities determined via two-dimensional NMR spectroscopy (NOESY, COSY, TOCSY) were utilized to position Et 743 in the minor groove of the oligonucleotide. Models of the ET 743-DNA adduct were generated using solvated mol. dynamics (AMBER version 4.1) that are consistent with the NMR data. The A and B units of Et 743 are oriented to the 5' and 3' side, resp., of the GN2 alkylation site and interact with the unalkylated oligonucleotide strand. The positions of the A and B units, as well as four hydrogen bonding interactions, direct unit C centrally out of the minor groove, thereby restricting its interactions with either side of the minor groove. The authors models suggest that the A and B units are responsible for DNA recognition and bonding and that unit C is the site for chemical modifications of et 743 in the development of new antitumor agents.

L27 ANSWER 63 OF 76 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:100940 HCAPLUS
DOCUMENT NUMBER: 126:112679
TITLE: Progress in the acquisition of new marine-derived anticancer compounds: development of ecteinascidin-743 (ET-743)
AUTHOR(S): Jimeno, Jose M.; Faircloth, Glynn; Cameron, Lewis; Meely, Kathleen; Vega, Eduardo; Gomez, Andres; Sousa-Faro, Jose Ma Fernandez; Rinehart, Kenneth
CORPORATE SOURCE: Pharma Mar, S.A., Research and Development, Madrid, 28760, Spain
SOURCE: Drugs of the Future (**1996**), 21(11),

1155-1165
CODEN: DRFUD4; ISSN: 0377-8282
PUBLISHER: Prous
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
IT **114899-77-3P**, Ecteinascidin-743
RL: PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(progress in the acquisition of new marine-derived anticancer compds.: development of ecteinascidin-743 (ET-743))
RN 114899-77-3 HCAPLUS
CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



AB A review, with 65 refs., of the progress in the acquisition of new marine-derived anticancer compds. and development of ecteinascidin-743 (ET-743).

L27 ANSWER 64 OF 76 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1996:619109 HCAPLUS
DOCUMENT NUMBER: 126:16866
TITLE: Ecteinascidins: putative biosynthetic precursors and absolute stereochemistry
AUTHOR(S): Sakai, Ryuichi; Jares-Erijman, Elizabeth A.; Manzanares, Ignacio; Elipe, Maria V. Silva; Rinehart, Kenneth L.
CORPORATE SOURCE: Roger Adams Laboratory, University of Illinois, Urbana, IL, 61801, USA
SOURCE: Journal of the American Chemical Society (**1996**), 118(38), 9017-9023
CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER: American Chemical Society

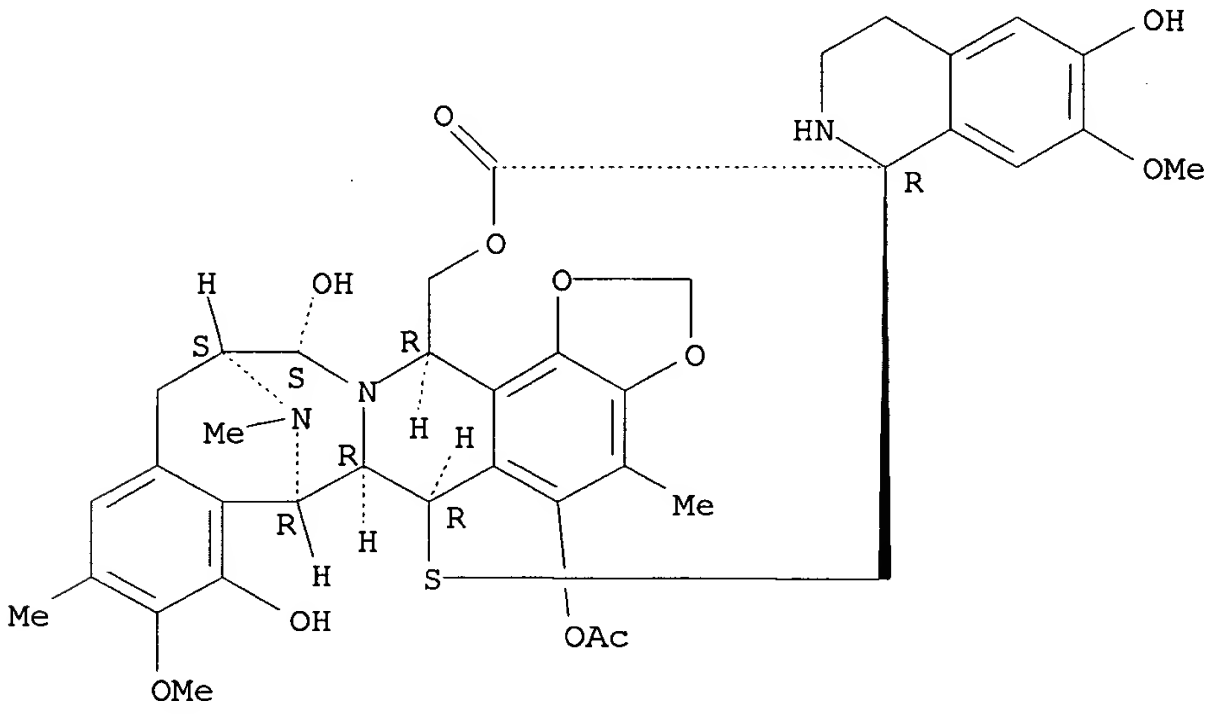
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **114899-77-3P**
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BSU (Biological study, unclassified); PRP (Properties); PUR (Purification or recovery); BIOL (Biological study); OCCU (Occurrence); PREP (Preparation)
(ecteinascidin isolation and structural characterization and activity from Caribbean tunicate)

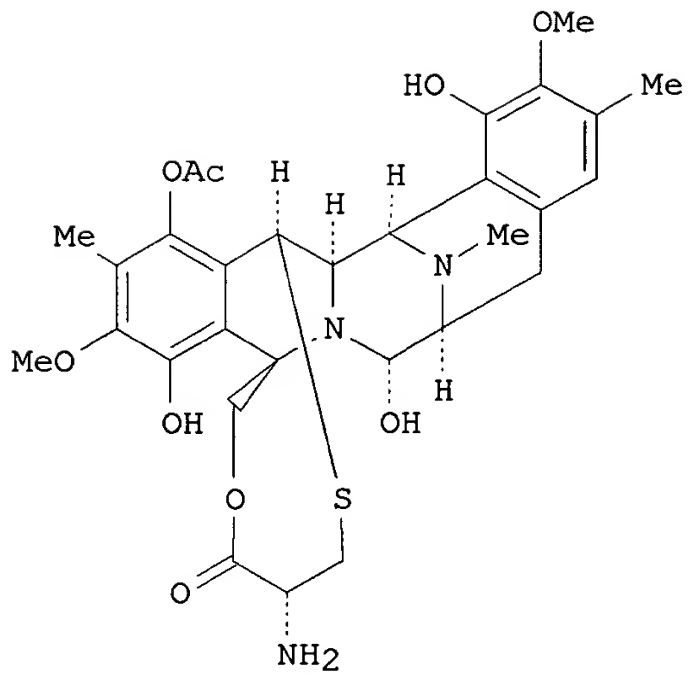
RN 114899-77-3 HCAPLUS

CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



GI

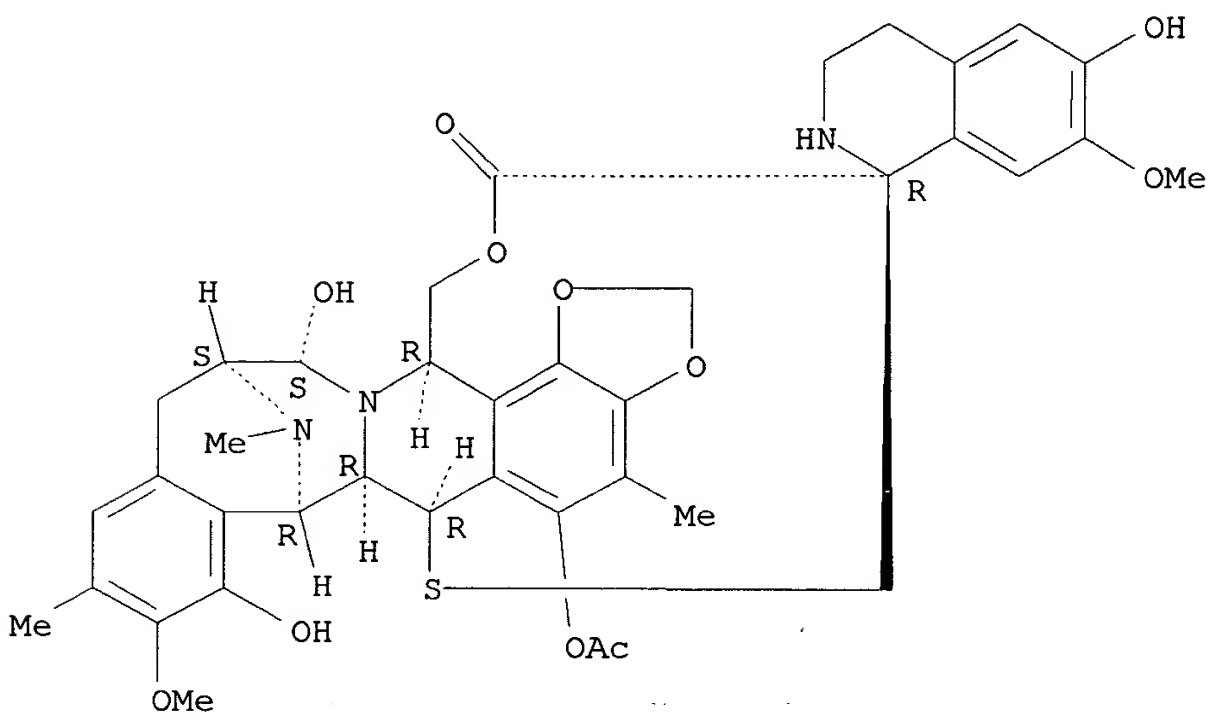


I

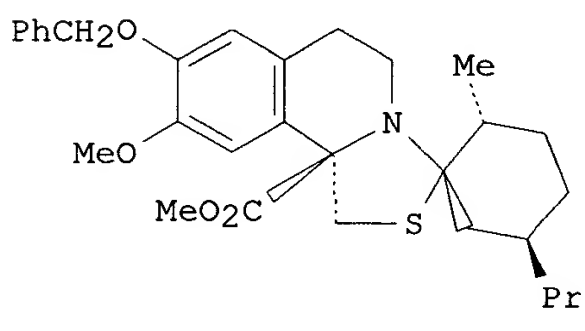
AB New bioactive ecteinascidins (Et's) 597 (I), 583, 594, and 596, putative biosynthetic precursors of previously described Et's [e.g., Et 743], were isolated from the Caribbean tunicate Ecteinascidia turbinata. Structures assigned to these compds. based on spectroscopic data represent a novel series of Et's with L-cysteine or its α-oxo analog as unit C. The absolute configuration of the L-Cys unit of I was assigned by chiral GC, while a 2D ROESY spectrum of its acetyl derivative completed the assignment of the stereochem. of I as 1R,2R,3R,4R,11R,13S,21S,1'R.

L27 ANSWER 65 OF 76 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1996:617832 HCAPLUS
DOCUMENT NUMBER: 126:19093
TITLE: Convergent enantioselective synthesis of the tetrahydroisoquinoline unit in the spiro ring of ecteinascidin 743
AUTHOR(S): Corey, E. J.; Gin, David Y.
CORPORATE SOURCE: Dep. Chem. Chem. Biol., Harvard Univ., Cambridge, MA, 01238, USA
SOURCE: Tetrahedron Letters (**1996**), 37(40), 7163-7166
CODEN: TELEAY; ISSN: 0040-4039
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 126:19093
IT **114899-77-3P**
RL: PNU (Preparation, unclassified); PREP (Preparation)
(convergent enantioselective synthesis of tetrahydroisoquinoline unit in spiro ring of ecteinascidin 743)
RN 114899-77-3 HCAPLUS
CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



GI



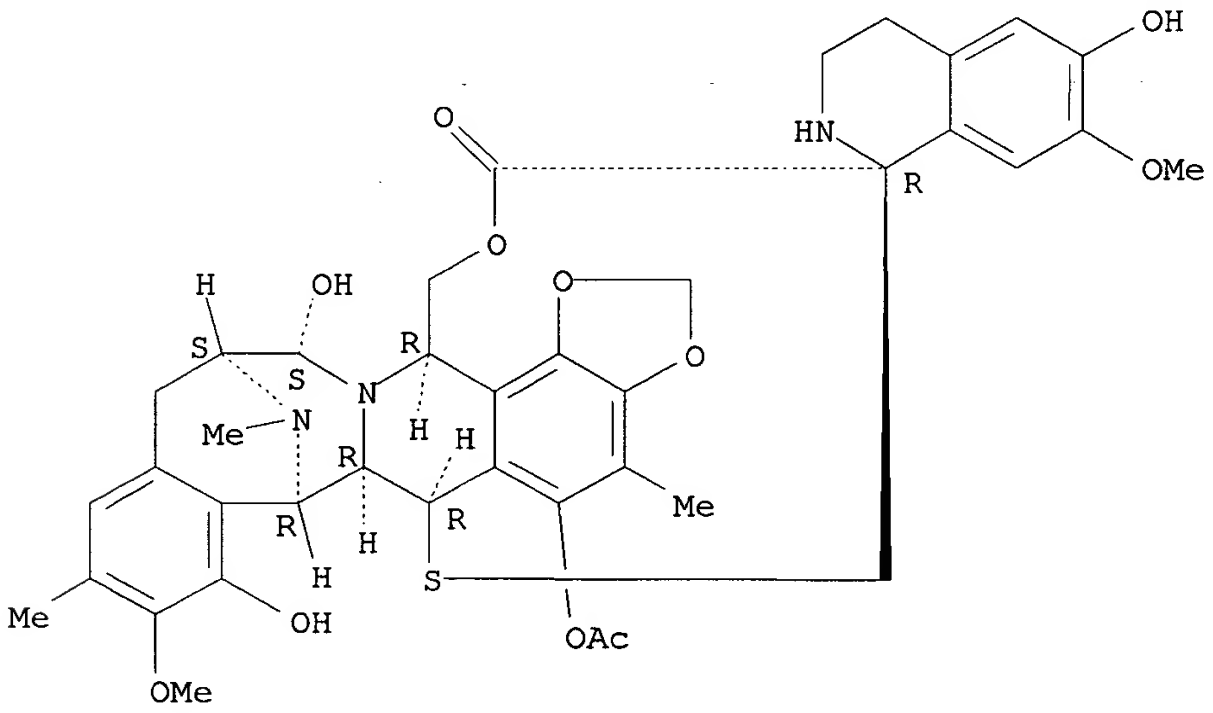
Pr-i I

AB An efficient enantioselective synthesis of the spiro tetrahydroisoquinoline I unit in ecteinascidin 743 is described, employing (+)-tetrahydrocarvone as a readily available and recoverable chiral auxiliary. The synthetic sequence involves a triply-convergent stereoselective bisannulation to construct the tetrahydroisoquinoline framework.

L27 ANSWER 66 OF 76 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1996:580617 HCAPLUS
DOCUMENT NUMBER: 125:237833
TITLE: DNA Sequence- and Structure-Selective Alkylation of Guanine N2 in the DNA Minor Groove by Ecteinascidin 743, A Potent Antitumor Compound from the Caribbean Tunicate Ecteinascidia turbinata
AUTHOR(S): Pommier, Yves; Kohlhagen, Glenda; Bailly, Christian; Waring, Michael; Mazumder, Abhijit; Kohn, Kurt W.
CORPORATE SOURCE: Division of Basic Science, National Cancer Institute, Bethesda, MD, USA
SOURCE: Biochemistry (**1996**), 35(41), 13303-13309
CODEN: BICHAW; ISSN: 0006-2960
PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal
LANGUAGE: English
IT **114899-77-3**, Ecteinascidin 743
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(DNA sequence- and structure-selective alkylation of guanine N2 in DNA minor groove by potent antitumor compound from Caribbean tunicate Ecteinascidia turbinata ecteinascidin 743)
RN 114899-77-3 HCAPLUS
CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

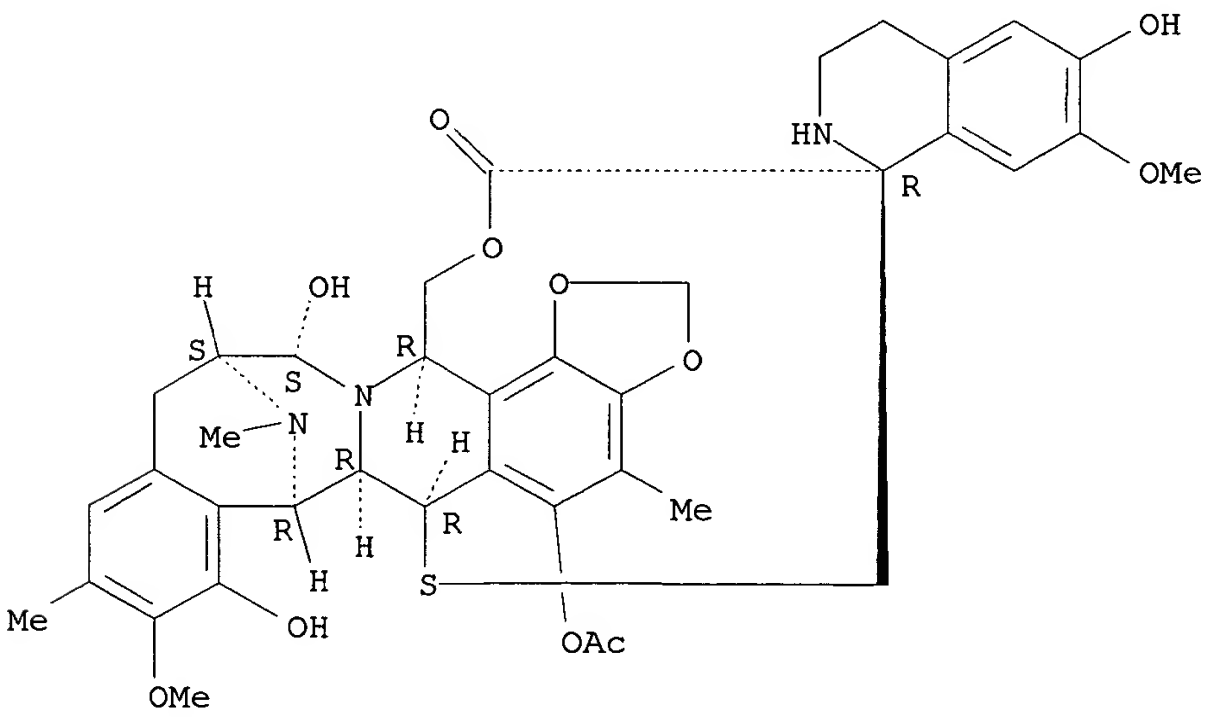


AB Ecteinascidin 743 is one of several related marine alkaloids isolated from the Caribbean tunicate Ecteinascidia turbinata. It is remarkably active and potent in a variety of in vitro and in vivo systems and has been selected for development as an anticancer agent. The present study investigates the interactions of ecteinascidin 743 with DNA. Ecteinascidin 743 retarded the electrophoretic migration of both supercoiled and relaxed simian virus 40 DNA even in the presence of SDS and after ethanol precipitation, consistent with covalent DNA modifications. Similar results were obtained in a DNA oligonucleotide derived from ribosomal DNA. However, DNA denaturation reversed the DNA modifications. The homopolymeric oligonucleotide dG/dC was modified while neither the dI/dC nor the dA/dT oligonucleotides were, consistent with covalent attachment of ecteinascidin 743 to the exocyclic amino group at position 2 of guanine. Ecteinascidin 743 was then compared to another known DNA minor groove alkylating agent, anthramycin, which has also been shown to alkylate guanine N2. Footprinting analyses with DNase I and 1,10-phenanthroline-copper and exonuclease III digestions showed that ecteinascidin 743 covers three to five bases of DNA and exhibits a different sequence specificity than anthramycin in the Escherichia coli

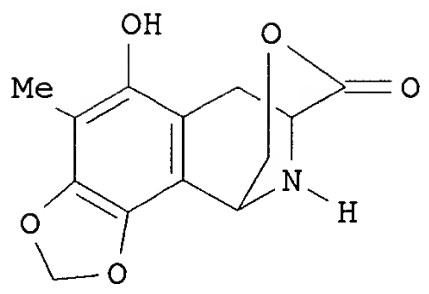
tyrosine tRNA promoter (tyrT DNA). The binding of ecteinascidin to DNA was abolished when guanines were substituted with inosines in this promoter. A band shift assay was designed to evaluate the influence of the bases flanking a centrally located guanine in an oligonucleotide containing inosines in place of guanines elsewhere. Ecteinascidin 743 and anthramycin showed similarities as well as differences in sequence selectivity. Ecteinascidin 743-guanine adducts appeared to require at least one flanking guanine and were strongest when the flanking guanine was 3' to the targeted guanine. These data indicate that ecteinascidin 743 is a novel DNA minor groove, guanine-specific alkylating agent.

L27 ANSWER 67 OF 76 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1996:544207 HCAPLUS
DOCUMENT NUMBER: 125:248206
TITLE: Enantioselective Total Synthesis of Ecteinascidin 743
AUTHOR(S): Corey, E. J.; Gin, David Y.; Kania, Robert S.
CORPORATE SOURCE: Department of Chemistry, Harvard University, Cambridge, MA, 02138, USA
SOURCE: Journal of the American Chemical Society (**1996**), 118(38), 9202-9203
CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **114899-77-3P**, Ecteinascidin 743
RL: SPN (Synthetic preparation); PREP (Preparation)
(enantioselective total synthesis of ecteinascidin 743)
RN 114899-77-3 HCAPLUS
CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (9CI) (CA INDEX NAME)

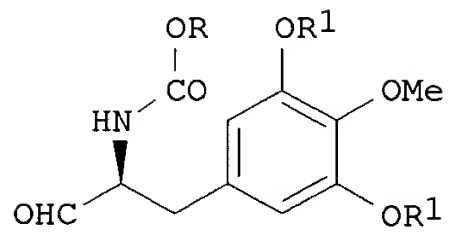
Absolute stereochemistry. Rotation (-).



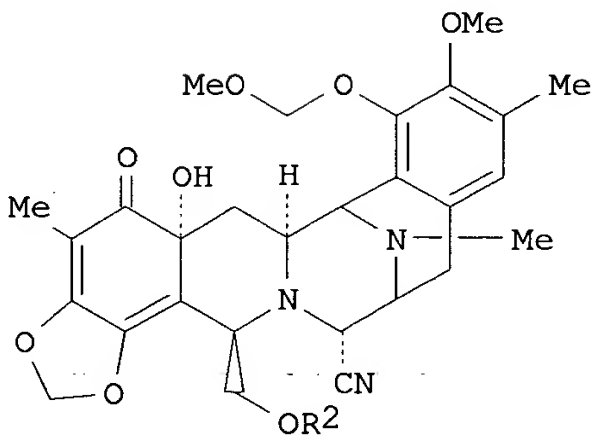
GI



I



II



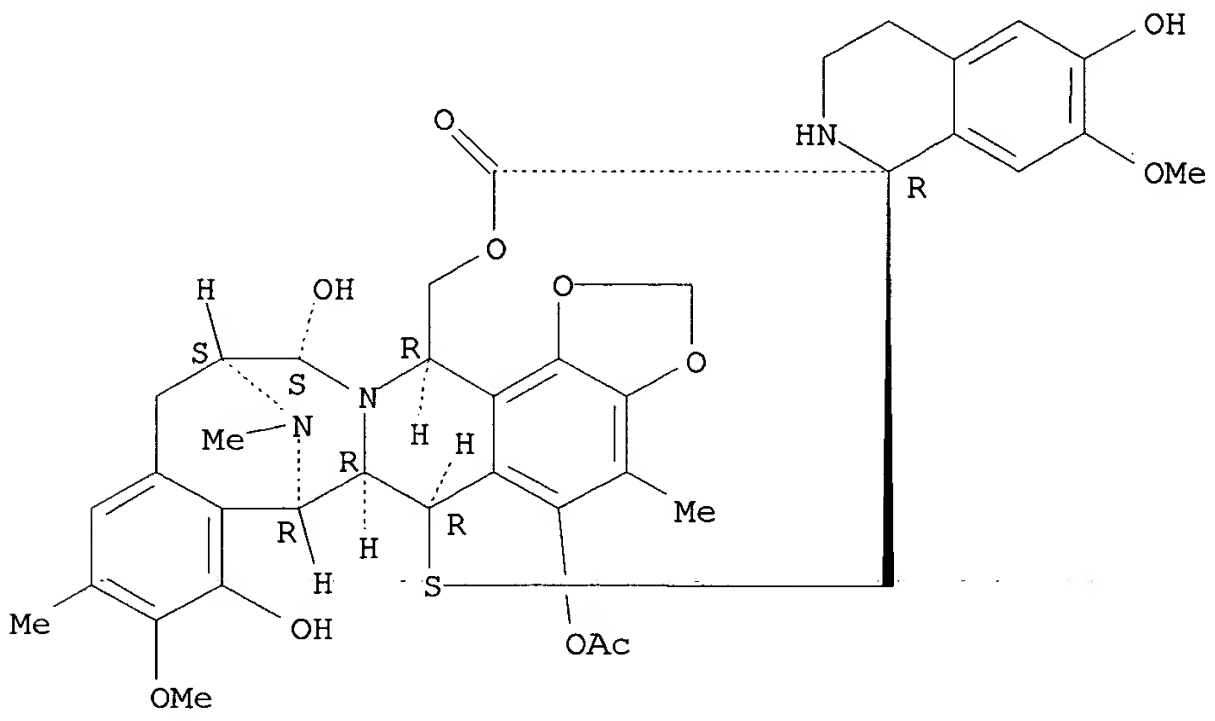
III

AB A compact, enantioselective synthesis of ecteinascidin 743 was reported starting from the building blocks I, II (R = allyl, R1 = SiMe2CMe3), 2-(3-hydroxy-4-methoxyphenyl)ethylamine, and N-allyloxycarbonyl-S-(9-fluorenylmethyl)cysteine via the formation and intramol. cyclization of the intermediate cysteine ester III (R2 = N-allyloxycarbonyl-S-(9-fluorenylmethyl)-L-cysteinyl).

L27 ANSWER 68 OF 76 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1996:316274 HCAPLUS
DOCUMENT NUMBER: 125:48529
TITLE: Characterization of antimitotic products from marine organisms that disorganize the microtubule network: Ecteinascidin 743, isohomohalichondrin-B and LL-15
AUTHOR(S): Garcia-Rocha, M.; Garcia-Gravalos; Avila, J.
CORPORATE SOURCE: Centro de Biologia Molecular "Severo Ochoa", Universidad Autonoma de Madrid, Madrid, 28049, Spain
SOURCE: British Journal of Cancer (**1996**), 73(8), 875-883
CODEN: BJCAAI; ISSN: 0007-0920
PUBLISHER: Stockton
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **114899-77-3**, Ecteinascidin 743
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(characterization of antimitotic products from marine organisms that disorganize the microtubule network: ecteinascidin 743, isohomohalichondrin-B and LL-15)
RN 114899-77-3 HCAPLUS
CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-

dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (9CI) (CA INDEX NAME)

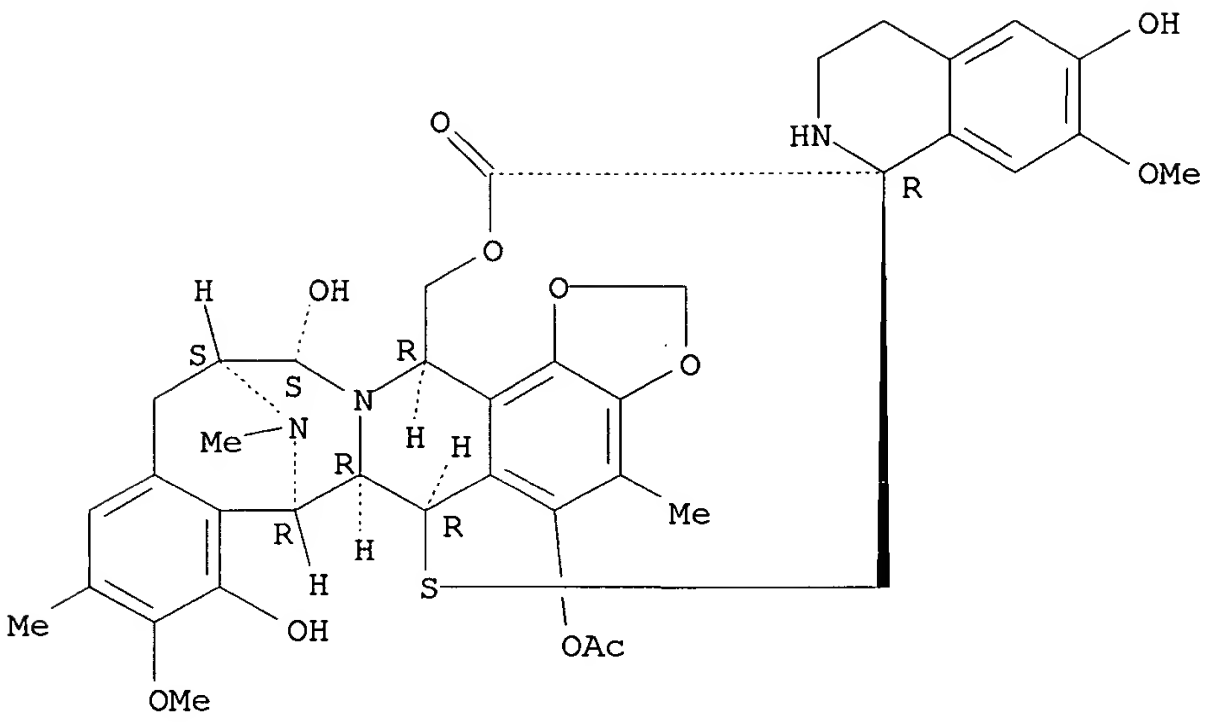
Absolute stereochemistry. Rotation (-).



AB The effect of selected marine compds. with antitumor activity on the cell microtubule network was tested by immunofluorescence analyses, or by other in vitro analyses involving competition with colchicine or with GTP for tubulin binding and tubulin polymerization, studies that were carried out in parallel with other microtubule poisons used as controls. Three compds. were found to disorganize the microtubule network: isohomohalichondrin B, LL-15 and ecteinascidin 743. The first two compds. prevent microtubule assembly and GTP binding to tubulin. Ecteinascidin 743 disorganizes the microtubule network but it does not seem to interact directly with tubulin.

L27 ANSWER 69 OF 76 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1996:270598 HCAPLUS
DOCUMENT NUMBER: 125:33930
TITLE: Synthetic studies on ecteinascidin 743
AUTHOR(S): Jow, Chung-Kuang
CORPORATE SOURCE: Rice Univ., Houston, TX, USA
SOURCE: (**1996**) 176 pp. Avail.: Univ. Microfilms Int., Order No. DA9610657
From: Diss. Abstr. Int., B 1996, 56(12), 6747
DOCUMENT TYPE: Dissertation
LANGUAGE: English
IT **114899-77-3P**, Ecteinascidin 743
RL: PNU (Preparation, unclassified); PREP (Preparation)
(synthesis of ecteinascidin 743)
RN 114899-77-3 HCAPLUS
CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (9CI) (CA INDEX NAME)

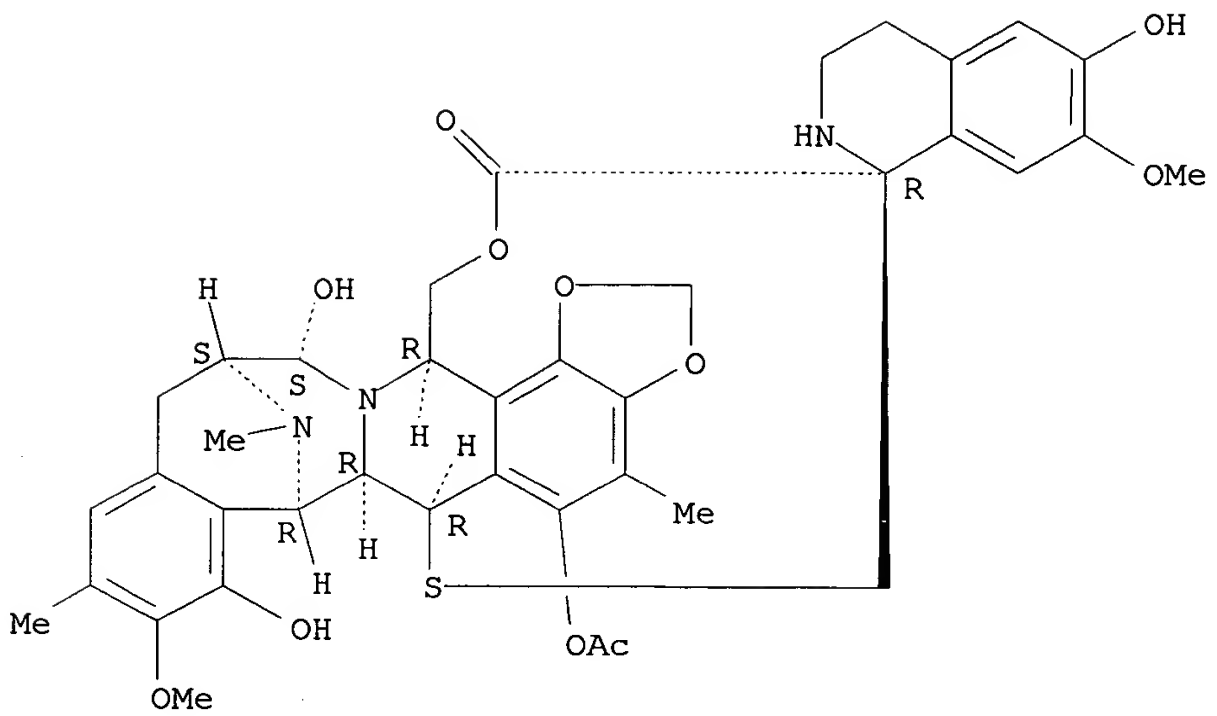
Absolute stereochemistry. Rotation (-).



AB Unavailable

L27 ANSWER 70 OF 76 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1995:1004450 HCAPLUS
DOCUMENT NUMBER: 124:56387
TITLE: Biosynthetic studies of ecteinascidins in the marine tunicate Ecteinascidia turbinata
AUTHOR(S): Kerr, Russell G.; Miranda, Neil F.
CORPORATE SOURCE: Dep. Chem., Florida Atlantic Univ., Boca Raton, FL, 33431-0991, USA
SOURCE: Journal of Natural Products (**1995**), 58(10), 1618-21
CODEN: JNPRDF; ISSN: 0163-3864
PUBLISHER: American Society of Pharmacognosy
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **114899-77-3**, Ecteinascidin 743
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); OCCU (Occurrence)
(biosynthetic studies of ecteinascidins in marine tunicate)
RN 114899-77-3 HCAPLUS
CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



AB A viable cell-free extract of the marine tunicate E. turbinata was generated that is capable of transforming amino acids into the ecteinascidin antitumor alkaloids. Tyrosine and cysteine were identified as 2 building blocks used in ecteinascidin production The enzyme prepns. in the in vitro studies were fortified with ATP, Mg2+, NADH, and NADPH.

L27 ANSWER 71 OF 76 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1994:400935 HCAPLUS
DOCUMENT NUMBER: 121:935
TITLE: Compositions comprising ecteinascidins and a method of treating herpes simplex virus infections and tumors therewith
INVENTOR(S): Rinehart, Kenneth; Ryuichi, Sakai; Holt, Tom G.
PATENT ASSIGNEE(S): Board of Trustees of the University of Illinois, USA
SOURCE: U.S., 18 pp. Cont.-in-part of U.S. 5,149,804.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

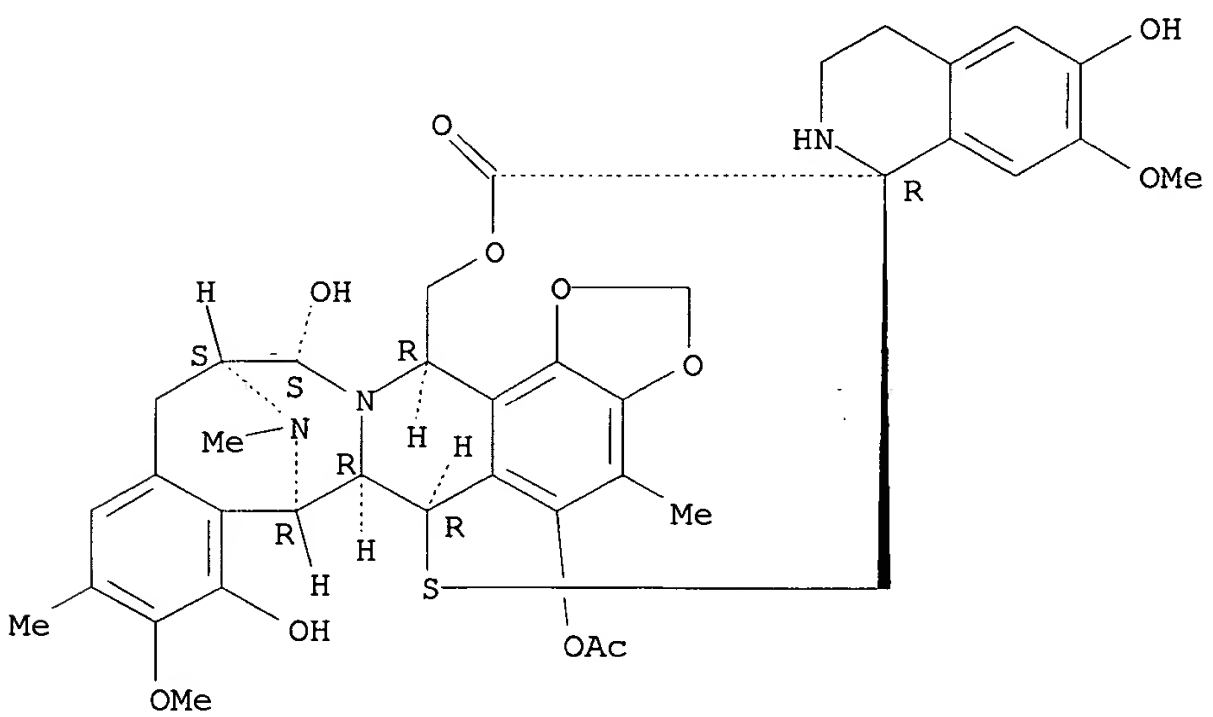
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5256663	A	19931026	US 1992-838149	19920218 <--
US 5089273	A	19920218	US 1990-548060	19900705 <--
US 5149804	A	19920922	US 1990-620427	19901130 <--

PRIORITY APPLN. INFO.:
US 1986-872189 B2 19860609
US 1986-898906 B2 19860821
US 1987-6395 B2 19870123
US 1987-1226 A1 19870601
US 1988-278629 B2 19881201
US 1990-548060 A2 19900705
US 1990-620427 A2 19901130

IT **114899-77-3**, Ecteinascidin 743
RL: BIOL (Biological study)
(isolation and characterization of, for herpes simplex 1 virus

infection treatment or antitumor agent)
RN 114899-77-3 HCAPLUS
CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

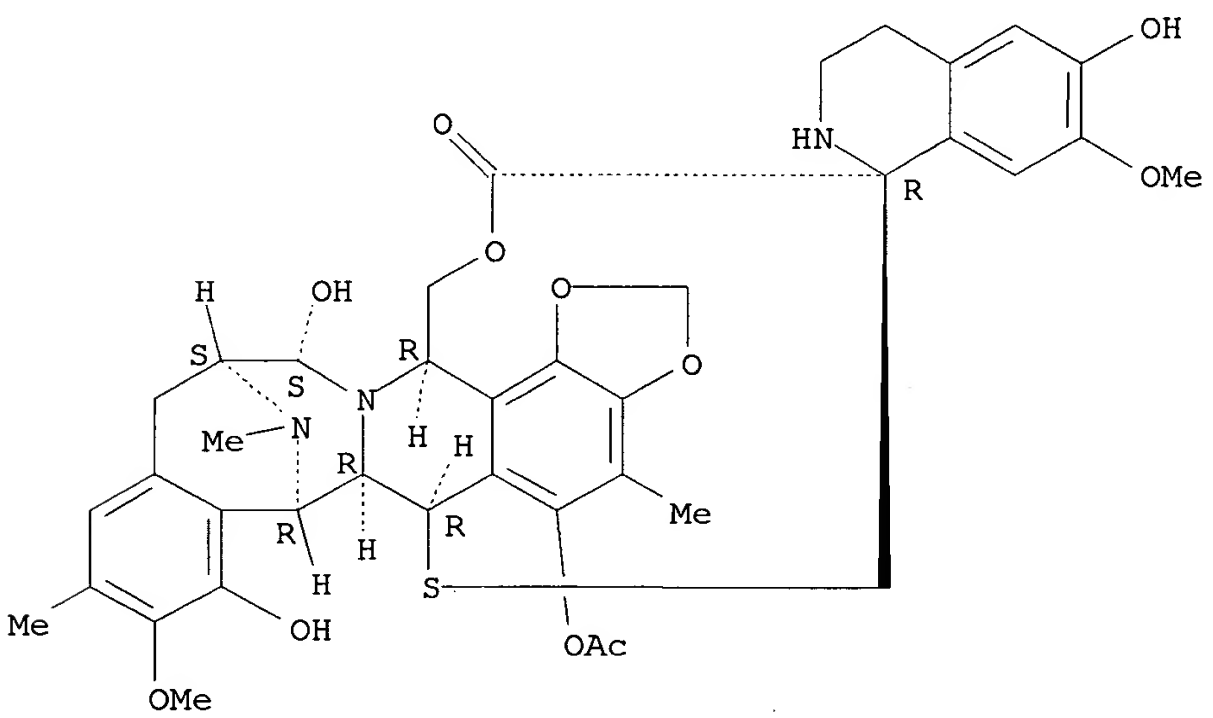


AB Pharmaceutical compns. are disclosed comprising matter extracted from the well-known and readily available tropical marine invertebrate, Ecteinascidia turbinata, and designated herein as ecteinascidins, and to the use of such compns. as antibacterial, anti-viral, and/or antitumor agents in mammals. Several ecteinascidins are obtained and characterized.; activities against herpes simplex type 1 virus and against several types of tumor cells (P388 lymphoma, B16 melanoma, etc.) are included.

L27 ANSWER 72 OF 76 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1993:160639 HCAPLUS
DOCUMENT NUMBER: 118:160639
TITLE: Additional antitumor ecteinascidins from a Caribbean tunicate: Crystal structures and activities in vivo
AUTHOR(S): Sakai, Ryuichi; Rinehart, Kenneth L.; Guan, Yue; Wang, Andrew H. J.
CORPORATE SOURCE: Sch. Chem. Sci., Univ. Illinois, Urbana, IL, 61801, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (**1992**), 89(23), 11456-60
CODEN: PNASA6; ISSN: 0027-8424
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **114899-77-3**, Ecteinascidin 743
RL: BIOL (Biological study)
(of Ecteinascidia turbinata, isolation and structure of, antitumor

activity in relation to)
RN 114899-77-3 HCAPLUS
CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



AB Ecteinascidins (Ets), isolated from the Caribbean tunicate Ecteinascidia turbinata, protect mice against P388 leukemia, B16 melanoma, M5076 ovarian sarcoma, Lewis lung carcinoma, and the LX-1 human lung and MX-1 human mammary carcinoma xenografts. Crystal structures of two tris(tetrahydroisoquinoline) Ets were investigated with single crystals of the 21-O-methyl-N12-formyl derivative of Et 729 and the natural N12-oxide of Et 743. Representatives of an addnl. class of Ets, Et 722 and Et 736, isolated from the same organism, were assigned tetrahydro-β-carboline-substituted bis(tetrahydroisoquinoline) structures by NMR and fast atom bombardment mass spectra.

L27 ANSWER 73 OF 76 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1992:463016 HCAPLUS
DOCUMENT NUMBER: 117:63016
TITLE: Isolation and characterization and therapeutic use of ecteinascidins 729, 743, 745, 759a, 759b, and 770
INVENTOR(S): Rinehart, Kenneth L.; Holt, Tom G.
PATENT ASSIGNEE(S): University of Illinois, USA
SOURCE: U.S., 14 pp. Cont.-in-part of U.S. Ser. No. 278,629, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

US 5089273	A	19920218	US 1990-548060	19900705	<--
US 5256663	A	19931026	US 1992-838149	19920218	<--

PRIORITY APPLN. INFO.:

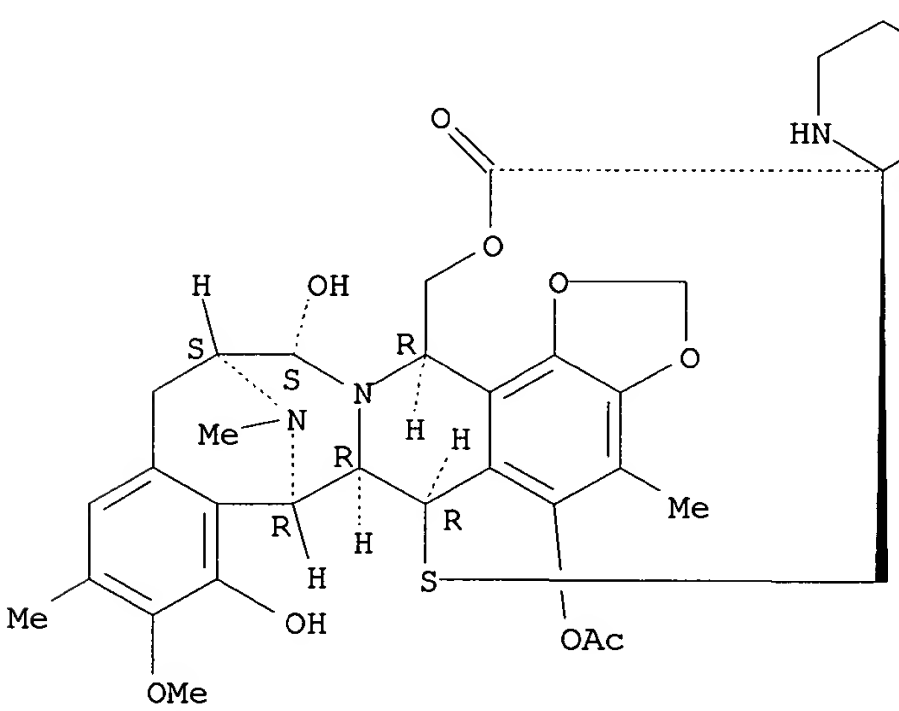
US 1986-872189	B2	19860609
US 1986-898906	B2	19860821
US 1987-6395	B2	19870123
US 1987-1226	A1	19870601
US 1988-278629	B2	19881201
US 1990-548060	A2	19900705
US 1990-620427	A2	19901130

IT **114899-77-3**, Ecteinascidin 743
RL: PROC (Process)
(isolation of, from Ecteinascidia turbinata, as antibacterial and antitumor agent)

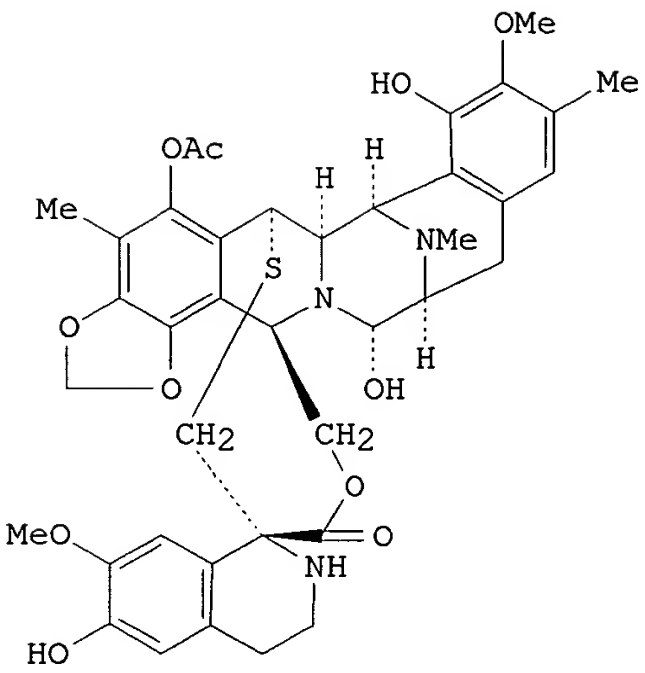
RN 114899-77-3 HCAPLUS

CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



GI

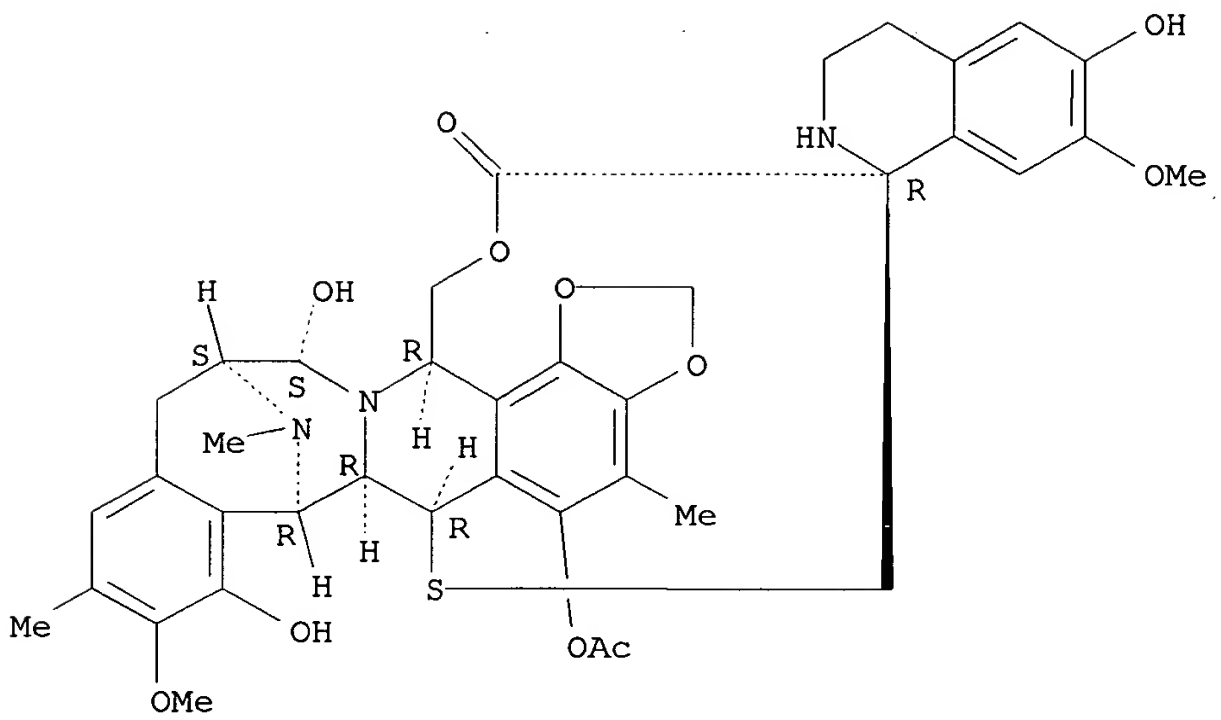


I

AB The title ecteinascidins are isolated form Ecteinascidia turbinata. The ecteinascidins are useful as antibacterial and/or antitumor agents in mammals. Preparation of derivs. of ecteinascidin 743 is also described. Structures for the ecteinascidins are presented, as are the antimicrobial spectrum of e.g. ecteinascidins 743 (I) and 745 and the antitumor activity of e.g. ecteinascidin 729 against P388 leukemia and B16 melanoma.

L27 ANSWER 74 OF 76 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1991:182423 HCAPLUS
DOCUMENT NUMBER: 114:182423
TITLE: Ecteinascidins 729, 743, 745, 759A, 759B, and 770: potent antitumor agents from the Caribbean tunicate Ecteinascidia turbinata [Erratum to document cited in CA113(9):75189d]
AUTHOR(S): Rinehart, Kenneth L.; Holt, Tom G.; Fregeau, Nancy L.; Stroh, Justin G.; Keifer, Paul A.; Sun, Furong; Li, Li H.; Martin, David G.
CORPORATE SOURCE: Sch. Chem. Sci., Univ. Illinois, Urbana, IL, 61801, USA
SOURCE: Journal of Organic Chemistry (**1991**), 56(4), 1676
CODEN: JOCEAH; ISSN: 0022-3263
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **114899-77-3**
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(of tunicate, isolation and mol. structure and antitumor activity of (Erratum))
RN 114899-77-3 HCAPLUS
CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (9CI) (CA INDEX NAME)

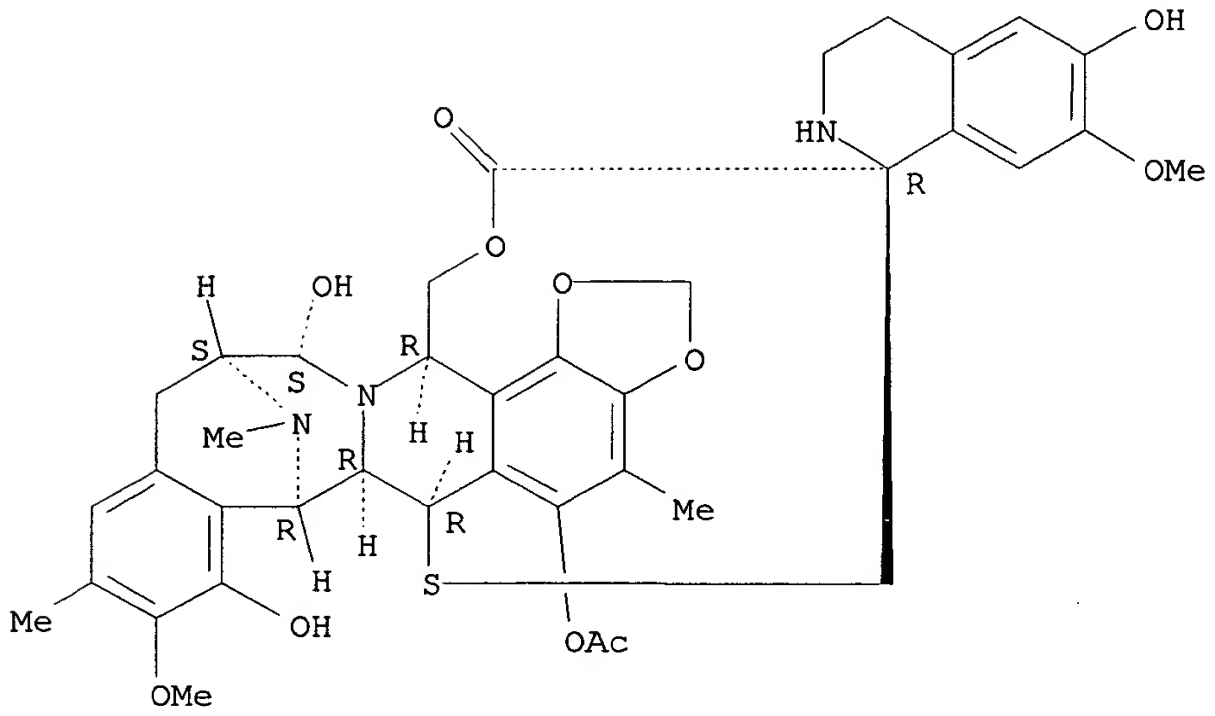
Absolute stereochemistry. Rotation (-).



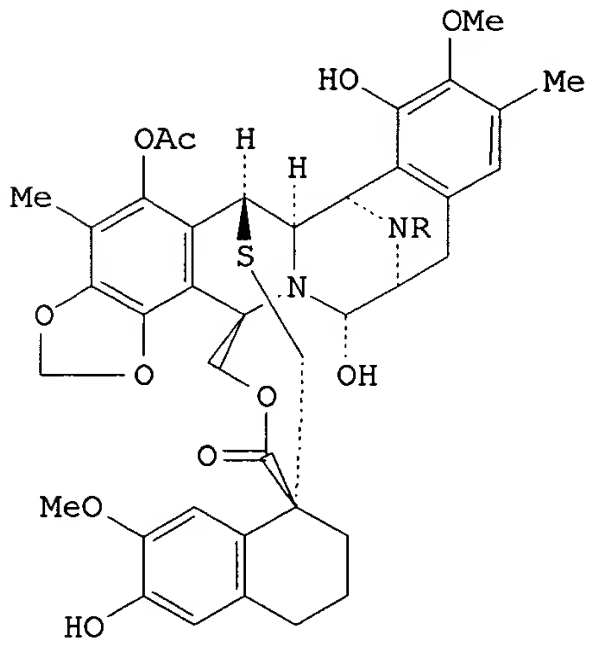
AB Errors in the text and reference 12 have been corrected Corrected Schemes I and II, unit
C, and structures 2-4 have been provided. The errors were not reflected in the abstract or the index entries.

L27 ANSWER 75 OF 76 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1990:456049 HCAPLUS
DOCUMENT NUMBER: 113:56049
TITLE: Antitumor tetrahydroisoquinoline alkaloids from the colonial ascidian Ecteinascidia turbinata
AUTHOR(S): Wright, Amy E.; Forleo, Dorilyn A.; Gunawardana, Geewananda P.; Gunasekera, Sarath P.; Koehn, Frank E.; McConnell, Oliver J.
CORPORATE SOURCE: Inst. Div. Biomed. Mar. Res., Harbor Branch Oceanogr., Ft. Pierce, FL, 34946, USA
SOURCE: Journal of Organic Chemistry (**1990**), 55(15), 4508-12
CODEN: JOCEAH; ISSN: 0022-3263
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **114899-77-3**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(of ascidian, islation and mol. structure and antitumor activity of)
RN 114899-77-3 HCAPLUS
CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



GI



I

AB A bioassay guided approach was used to isolate 2 antitumor tetrahydroisoquinoline alkaloids (I, R = H, Me) from the marine ascidian E. turbinata collected in the Caribbean. The structures were determined through spectroscopic methods. I inhibit replication of P388 murine leukemia in vitro with 50% IDs of 0.93 and 1.3 ng/mL., resp.

L27 ANSWER 76 OF 76 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1988:400811 HCAPLUS
DOCUMENT NUMBER: 109:811
TITLE: Purification and characterization of ecteinascidins 729, 743, 745, 759a, 759b, and 770 having antibacterial and antitumor properties
INVENTOR(S): Rinehart, Kenneth L.; Holt, Tom G.

PATENT ASSIGNEE(S): University of Illinois, USA
SOURCE: PCT Int. Appl., 32 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

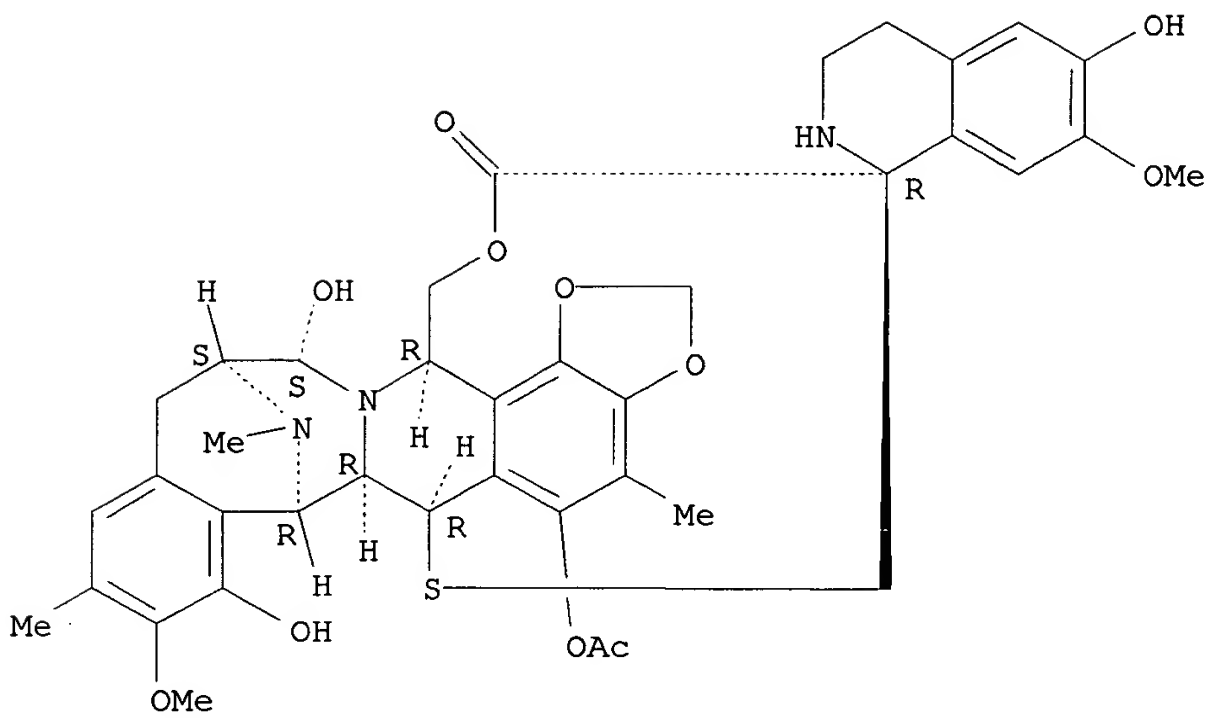
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
WO 8707610	A2	19871217	WO 1987-US1226	19870601	<--
WO 8707610	A3	19880225			
W: AU, DK, FI, JP, KR, NO, US, US, US					
RW: AT, BE, CH, DE, FR, GB, IT, LU, NL, SE					
AU 8775819	A1	19880111	AU 1987-75819	19870601	<--
AU 589282	B2	19891005			
EP 309477	A1	19890405	EP 1987-904158	19870601	<--
EP 309477	B1	19911106			
R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE					
JP 01502749	T2	19890921	JP 1987-503861	19870601	<--
JP 2562162	B2	19961211			
AT 69234	E	19911115	AT 1987-904158	19870601	<--
FI 8805726	A	19881209	FI 1988-5726	19881209	<--

PRIORITY APPLN. INFO.:

US 1986-872189	A2	19860609
US 1986-898906	A2	19860821
US 1987-6395	A2	19870123
EP 1987-904158	A	19870601
WO 1987-US1226	A	19870601

IT **114899-77-3P**
RL: PREP (Preparation)
(purification and characterization and antitumor and(or) antibacterial activity of, of Ecteinascidia turbinata,)
RN 114899-77-3 HCAPLUS
CN Spiro[6,16-(epithiopropanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, 5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethyl-, (1'R,6R,6aR,7R,13S,14S,16R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



AB The title compds. are isolated and purified from marine colonial tunicate Ecteinascidia turbinate and are characterized. The compds. have antibacterial properties and certain ones have cytotoxic and antitumor properties. Tunicate (30.5 kg weight) was extracted with MeOH which was partitioned by addition of 1 N aqueous NaNO3 and toluene. The aqueous phase was

extracted with CH2Cl2 which was dried, solubilized in MeOH and CH2Cl2, and triturated with hexane and CH2Cl2, and the CH2Cl2 triturate was purified by countercurrent chromatog., medium pressure liquid chromatog. on CHP-20, desalting, HPLC on Whatman Partisil 10 OD5-3 to give ecteinascidins 743 (27) and 745 (4.3 mg). These 2 compds. showed antibacterial activity against Micrococcus luteus in a disk diffusion assay (mass/disk 0.2 and 40 μg, resp. for zone of inhibition of 17 and 7 mm, resp.) and antitumor activity in a L1210 tube dilution assay (ID50 0.0005 and 0.088 μg/mL, resp. and ID90 0.0017 and 0.19 μg/mL, resp.) and P388 mouse leukemia test (0.063 mg 743/kg T/C toxic, 0.25 mg 745/Kg T/C .apprx.100).

=> log h

=> file stnguide

FILE 'STNGUIDE' ENTERED AT 14:26:40 ON 29 JAN 2004
USE IS SUBJECT TO THE TERMS OF YOUR CUSTOMER AGREEMENT
COPYRIGHT (C) 2004 AMERICAN CHEMICAL SOCIETY, JAPAN SCIENCE
AND TECHNOLOGY CORPORATION, AND FACHINFORMATIONSZENTRUM KARLSRUHE

FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Jan 23, 2004 (20040123/UP).

Headings for files used

=> file medline

FILE 'MEDLINE' ENTERED AT 14:26:44 ON 29 JAN 2004

FILE LAST UPDATED: 28 JAN 2004 (20040128/UP). FILE COVERS 1958 TO DATE.

On December 14, 2003, the 2004 MeSH terms were loaded. See HELP RLOAD for details.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2004 vocabulary. See http://www.nlm.nih.gov/mesh/ and http:\\www.nih.gov/pubs/yechbull/nd03/nd03_mesh.html for a description on changes.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> file embase

FILE 'EMBASE' ENTERED AT 14:26:50 ON 29 JAN 2004
COPYRIGHT (C) 2004 Elsevier Inc. All rights reserved.

FILE COVERS 1974 TO 22 Jan 2004 (20040122/ED)

EMBASE has been reloaded. Enter HELP RLOAD for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> file biosis

FILE 'BIOSIS' ENTERED AT 14:26:53 ON 29 JAN 2004
COPYRIGHT (C) 2004 BIOLOGICAL ABSTRACTS INC.(R)

FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 28 January 2004 (20040128/ED)

FILE RELOADED: 19 October 2003.

Note: Searching Registry Numbers for ETM 305, ETM 304, & ETM 775 yielded Ø hits in Medline, Embase, and Biosis.

=> file registry

FILE 'REGISTRY' ENTERED AT 14:26:58 ON 29 JAN 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2004 American Chemical Society (ACS)

Property values tagged with IC are from the ZIC/VINITI data file

provided by InfoChem.

STRUCTURE FILE UPDATES: 28 JAN 2004 HIGHEST RN 642928-00-5
DICTIONARY FILE UPDATES: 28 JAN 2004 HIGHEST RN 642928-00-5

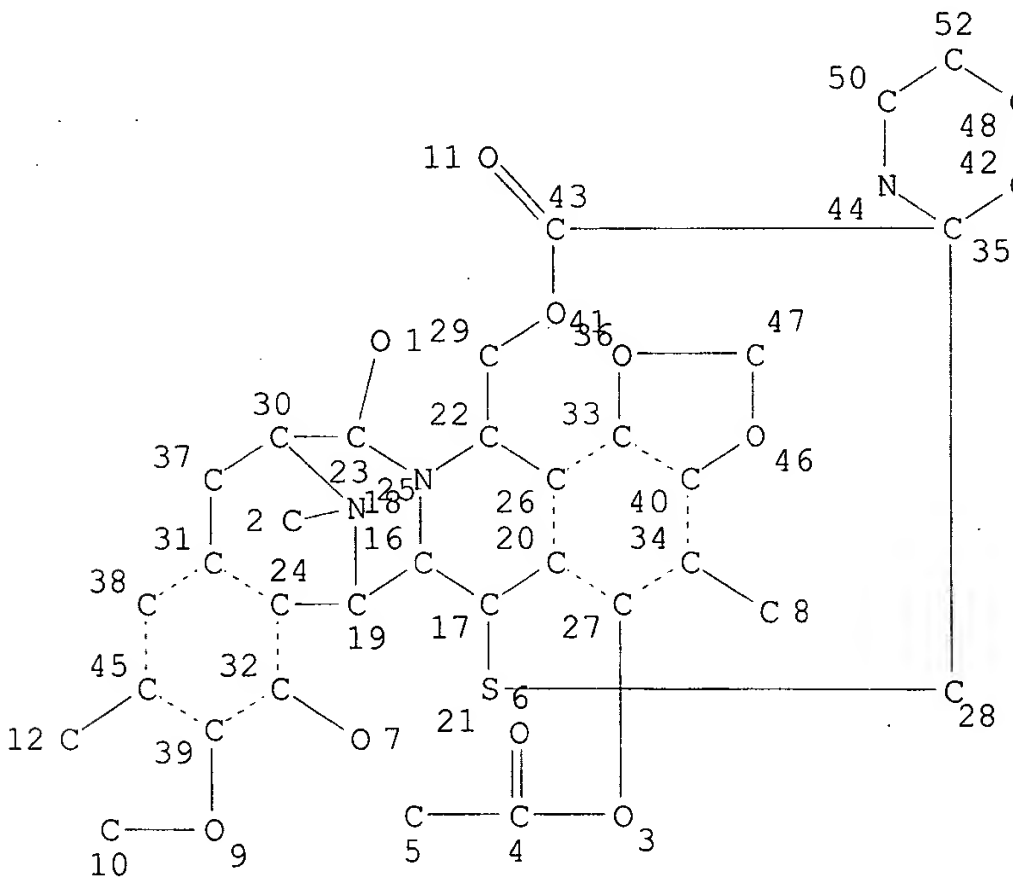
TSCA INFORMATION NOW CURRENT THROUGH JULY 14, 2003

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

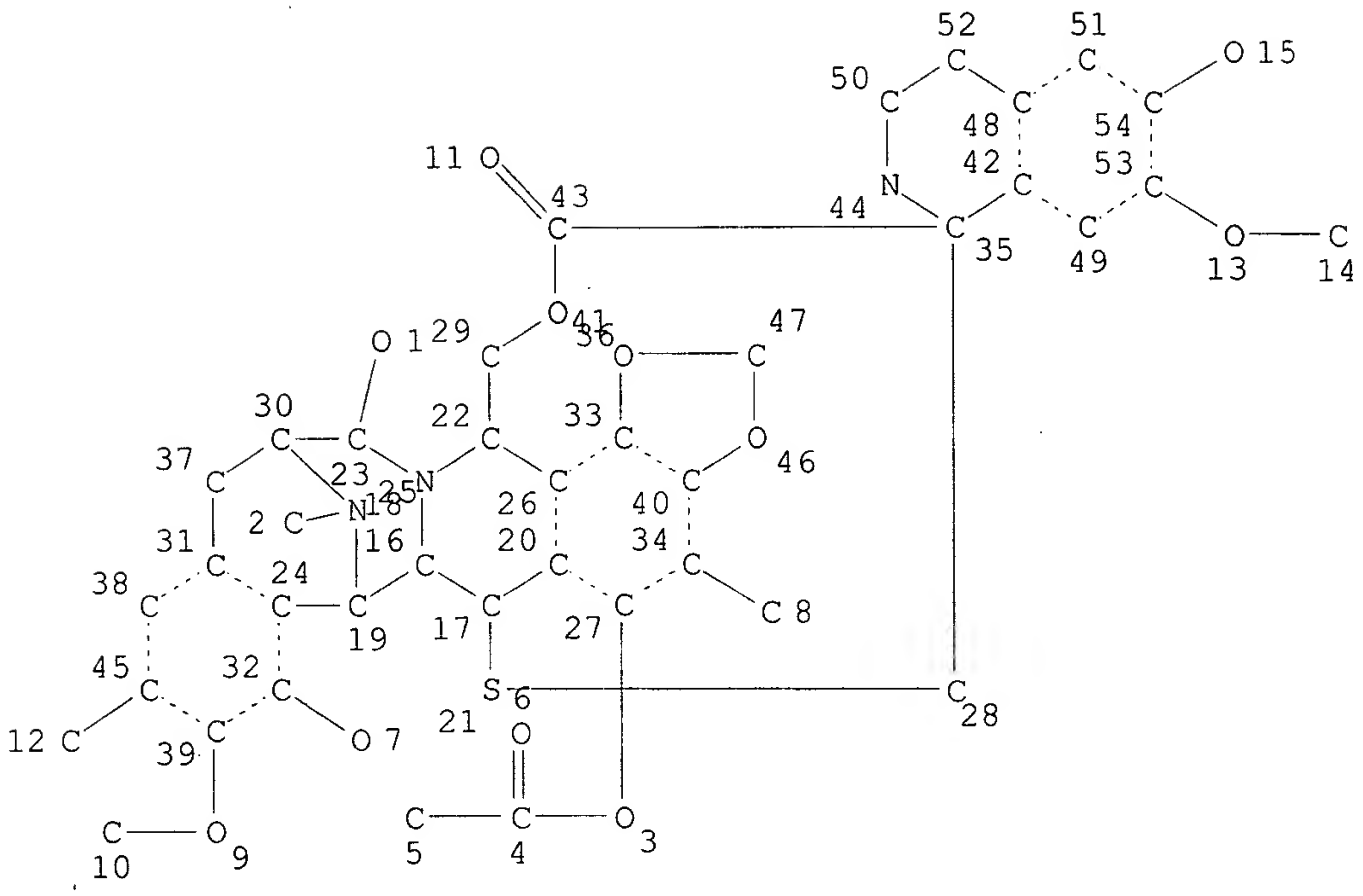
=> d que l56
L15 STR



NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 54

STEREO ATTRIBUTES: NONE
L16 4 SEA FILE=REGISTRY FAM FUL L15
L17 STR



NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 54

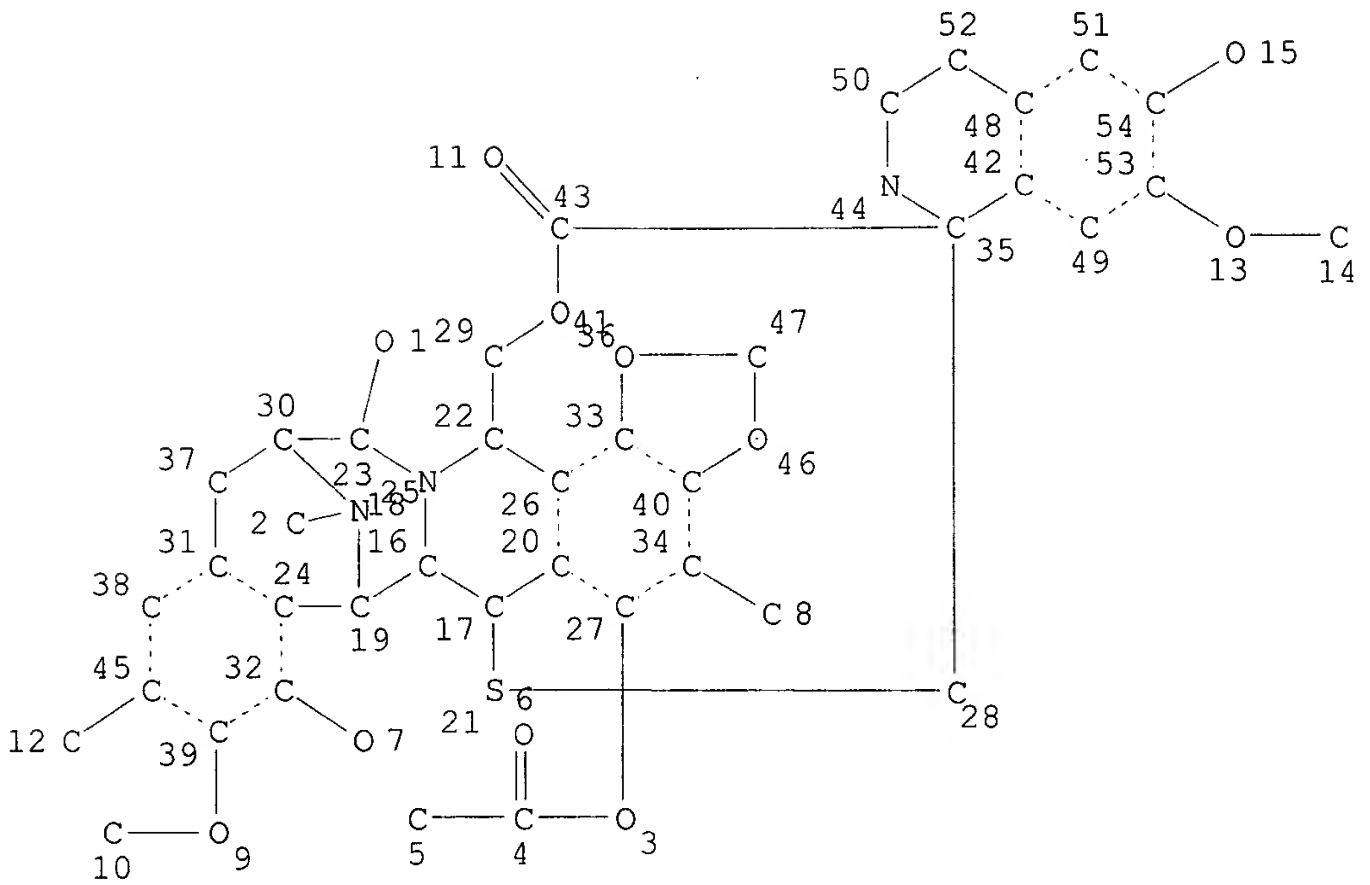
STEREO ATTRIBUTES: NONE

```
L18             2 SEA FILE=REGISTRY EXA FUL L17
L19             4 SEA FILE=REGISTRY ABB=ON  PLU=ON  L16 OR L18
L31            90 SEA FILE=MEDLINE ABB=ON   PLU=ON  L19
L50           116 SEA FILE=MEDLINE ABB=ON   PLU=ON  ECTEINASCIDIN
L51             7 SEA FILE=MEDLINE ABB=ON   PLU=ON  ECTEINASCIDIN (L) ?METABOL?
L53           116 SEA FILE=MEDLINE ABB=ON   PLU=ON  L31 OR L50
L55             1 SEA FILE=MEDLINE ABB=ON   PLU=ON  L53 (L) ME
L56             8 SEA FILE=MEDLINE ABB=ON   PLU=ON  L55 OR L51
```

search Registry numbers in Medline
} free text
ME — metabolism
Combine cites

=> d que l59
L15 STR

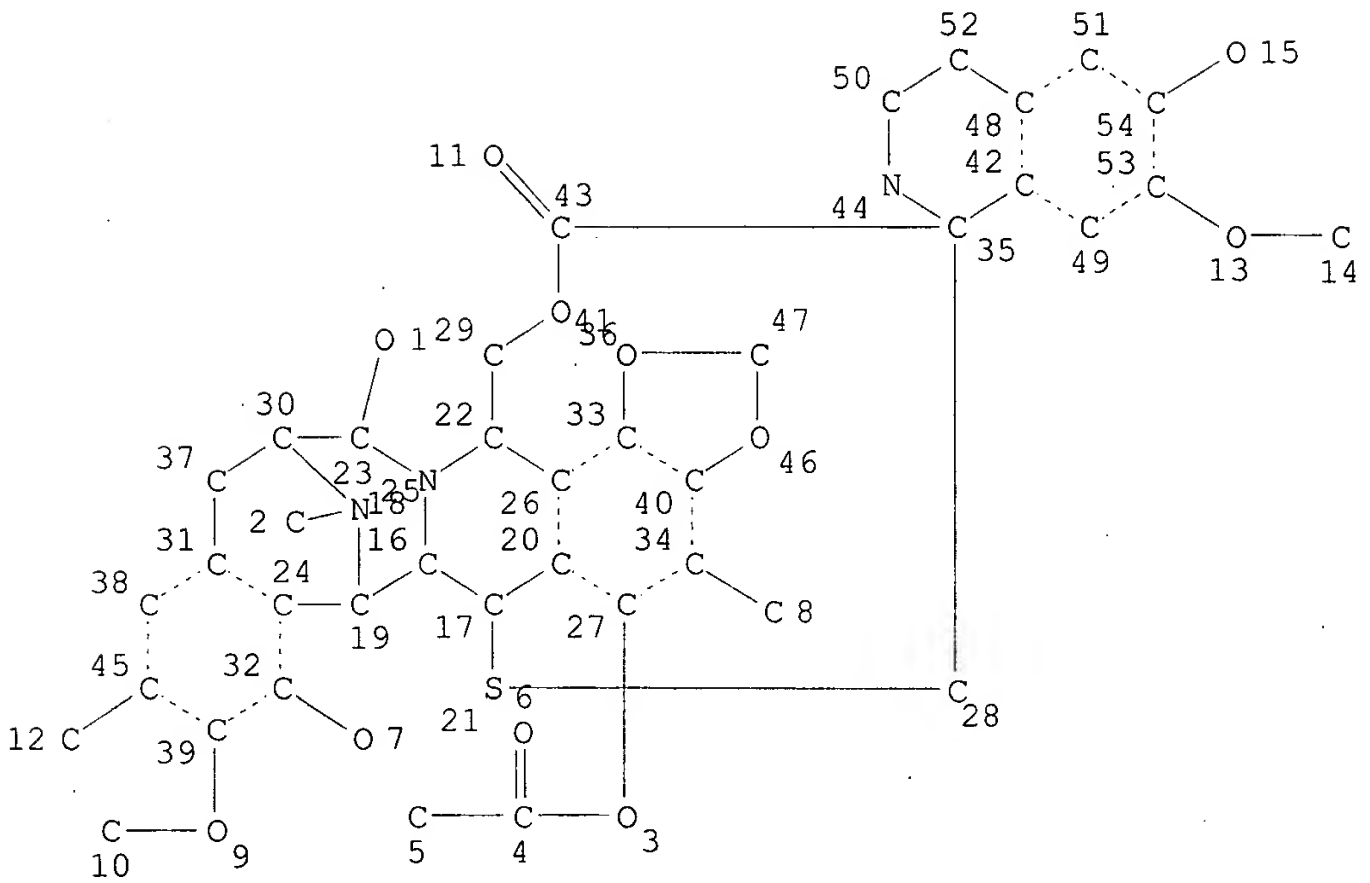
L15



NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 54

STEREO ATTRIBUTES: NONE
L16 4 SEA FILE=REGISTRY FAM FUL L15
L17 STR



NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 54

STEREO ATTRIBUTES: NONE

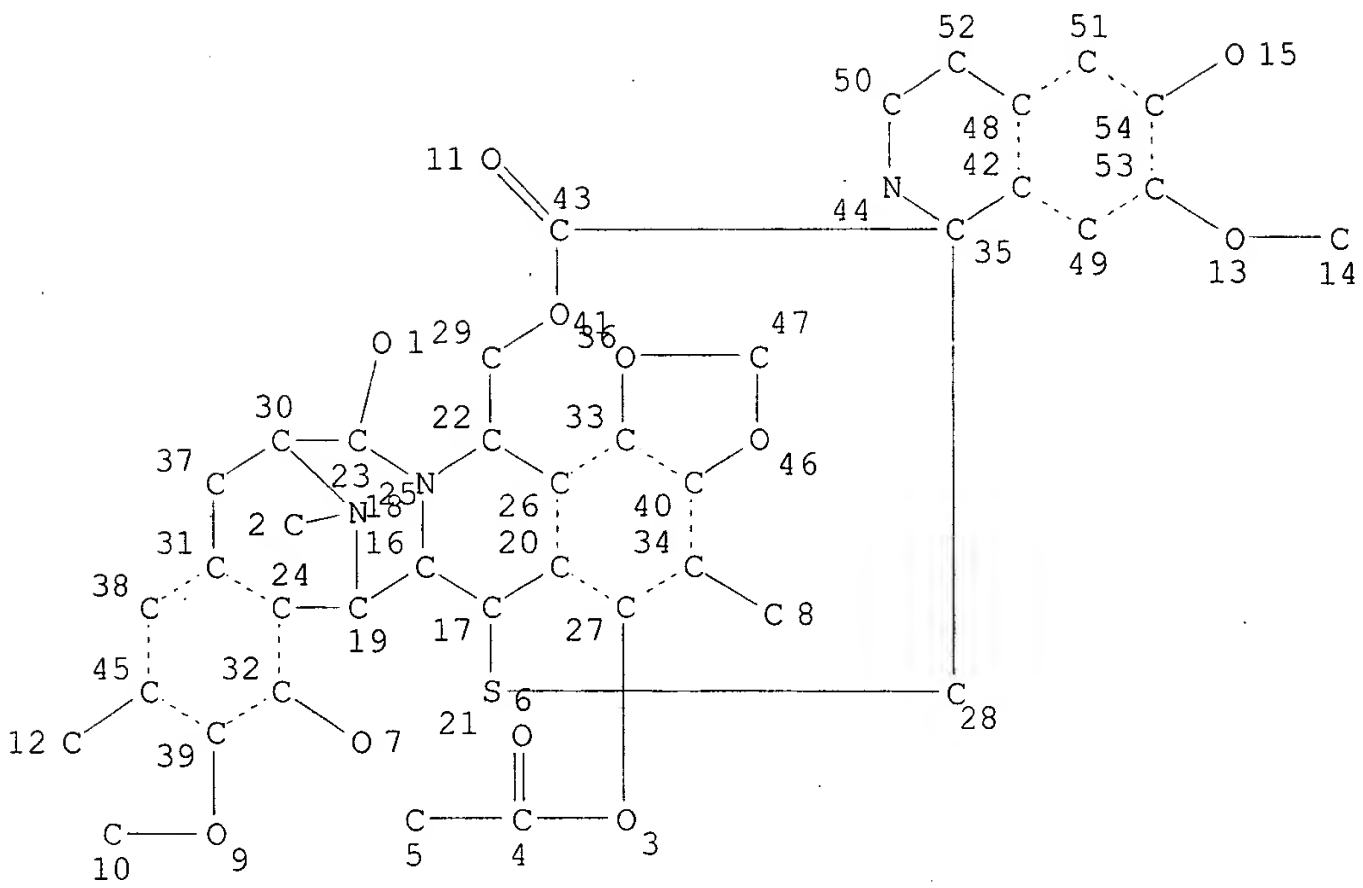
```
L18             2 SEA FILE=REGISTRY EXA FUL L17
L19             4 SEA FILE=REGISTRY ABB=ON  PLU=ON  L16 OR L18
L38           190 SEA FILE=EMBASE ABB=ON  PLU=ON  L19
L57           206 SEA FILE=EMBASE ABB=ON  PLU=ON  ECTEINASCIDIN
L58           207 SEA FILE=EMBASE ABB=ON  PLU=ON  L38 OR L57
L59             6 SEA FILE=EMBASE ABB=ON  PLU=ON  L58 (L) ?METABOL?
```

search eeg. #s in Embase

free text

```
=> d que l71
L15                 STR
```

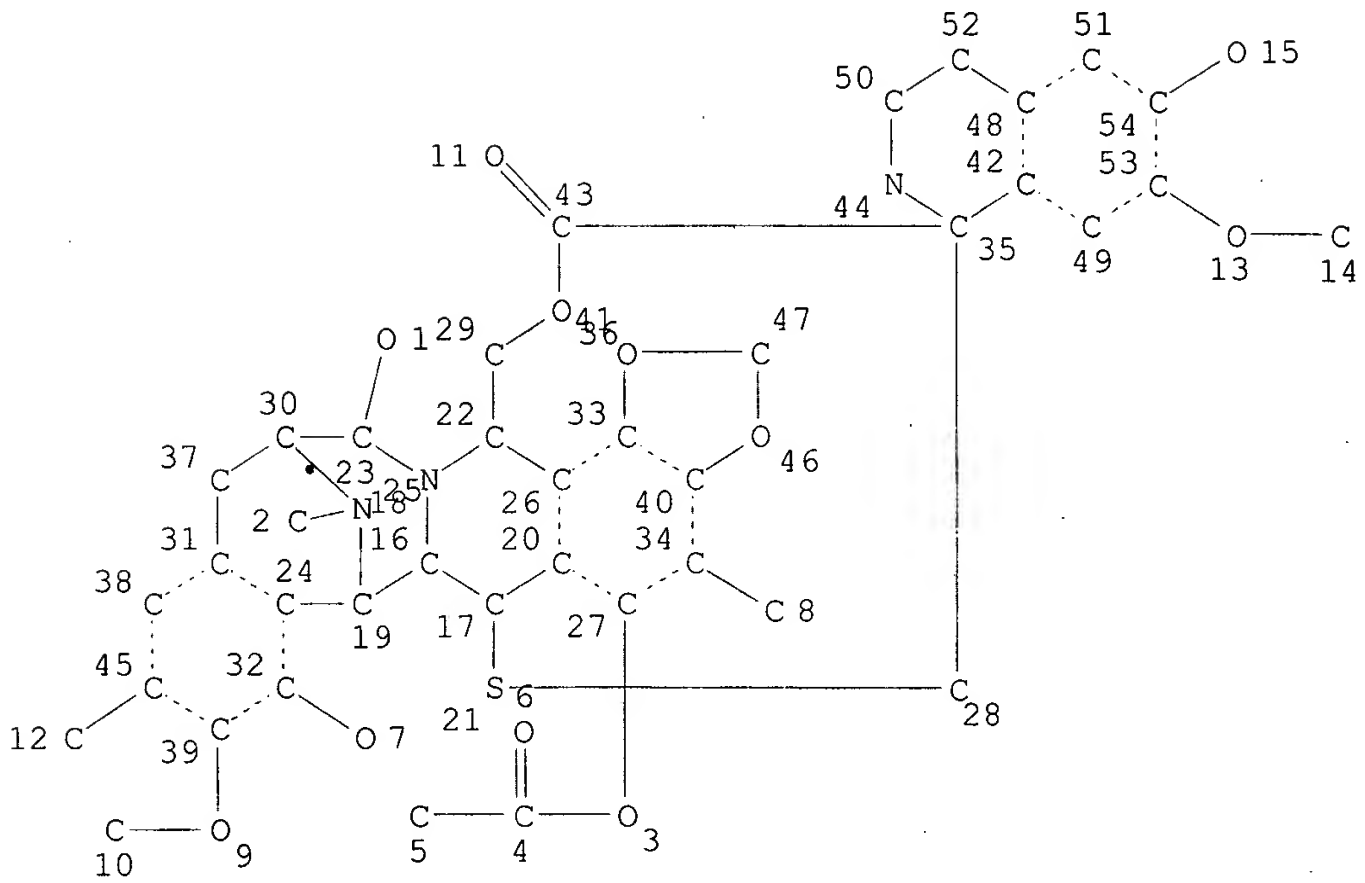
L15



NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 54

STEREO ATTRIBUTES: NONE
L16 4 SEA FILE=REGISTRY FAM FUL L15
L17 STR



NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 54

STEREO ATTRIBUTES: NONE

```
L18             2 SEA FILE=REGISTRY EXA FUL L17
L19             4 SEA FILE=REGISTRY ABB=ON  PLU=ON  L16 OR L18
L43           112 SEA FILE=BIOSIS ABB=ON  PLU=ON  L19
L60           152 SEA FILE=BIOSIS ABB=ON  PLU=ON  ECTEINASCIDIN
L61           158 SEA FILE=BIOSIS ABB=ON  PLU=ON  L43 OR L60
L62             8 SEA FILE=BIOSIS ABB=ON  PLU=ON  L61 (L) ?METABO?
L67             1 SEA FILE=BIOSIS ABB=ON  PLU=ON  "ETM 305"
L68             1 SEA FILE=BIOSIS ABB=ON  PLU=ON  "ETM 204"
L69             1 SEA FILE=BIOSIS ABB=ON  PLU=ON  "ETM 775"
L70             1 SEA FILE=BIOSIS ABB=ON  PLU=ON  (L67 OR L68 OR L69)
L71             8 SEA FILE=BIOSIS ABB=ON  PLU=ON  L70 OR L62
```

search Req.#s in Biosis

free text

Combine cites

```
=> file stnguide

FILE 'STNGUIDE' ENTERED AT 14:27:43 ON 29 JAN 2004
USE IS SUBJECT TO THE TERMS OF YOUR CUSTOMER AGREEMENT
COPYRIGHT (C) 2004 AMERICAN CHEMICAL SOCIETY, JAPAN SCIENCE
AND TECHNOLOGY CORPORATION, AND FACHINFORMATIONSZENTRUM KARLSRUHE

FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Jan 23, 2004 (20040123/UP).

=> dup rem l56 l59 l71
```

FILE 'MEDLINE' ENTERED AT 14:27:59 ON 29 JAN 2004

FILE 'EMBASE' ENTERED AT 14:27:59 ON 29 JAN 2004

FILE 'BIOSIS' ENTERED AT 14:27:59 ON 29 JAN 2004

PROCESSING COMPLETED FOR L56
PROCESSING COMPLETED FOR L59
PROCESSING COMPLETED FOR L71
L73 11 DUP REM L56 L59 L71 (11 DUPLICATES REMOVED)
ANSWERS '1-8' FROM FILE MEDLINE
ANSWERS '9-11' FROM FILE BIOSIS

Remove duplicates

=> d l73 bib ab 1-
YOU HAVE REQUESTED DATA FROM 11 ANSWERS - CONTINUE? Y/(N):y

L73 ANSWER 1 OF 11 MEDLINE on STN DUPLICATE 1
AN 2003523145 IN-PROCESS
DN PubMed ID: 14599461
TI Use of CFU-GM assay for prediction of human maximum tolerated dose of a new antitumoral drug: Yondelis (ET-743).
AU Gomez Susana G; Bueren Juan A; Faircloth Glynn; Albella Beatriz
CS PharmaMar, S.A. Poligono Industrial La Mina, Avda de los Reyes, 1. 28770 Colmenar Viejo, Madrid, Spain.
SO Toxicology in vitro : an international journal published in association with BIBRA, (2003 Oct-Dec) 17 (5-6) 671-4.
Journal code: 8712158. ISSN: 0887-2333.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS IN-PROCESS; NONINDEXED; Priority Journals
ED Entered STN: 20031106
Last Updated on STN: 20031219
AB Acute cytotoxic exposure causes decreases in bone marrow progenitors that precedes the neutrophil nadir. Experiments in animal models reveal a relationship between the reduction in granulocyte-macrophage progenitors (CFU-GM) and the decrease in absolute neutrophil count [Toxicol. Pathol. 21 (1993) 241]. Recently, the prevalidation of a model for predicting acute neutropenia by the CFU-GM assay has been reported [Toxicol. In Vitro 15 (2001) 729]. The model was based on prediction of human MTD by adjusting the animal-derived MTD for the differential sensitivity between CFU-GM from animal species and humans. In this study, this model has been applied on a new antitumoral drug, Yondelis (**Ecteinascidin;** ET-743). Preclinical studies showed that hematotoxicity was the main side effect in mice, being the MTD of 600 microg/m2 [Drugs Future 21 (1996) 1155]. The sensitivity of myeloid progenitors was higher in mice than in humans, with IC90 values of 0.69+/-0.22 nM and 1.31+/-0.21 nM for murine and human CFU-GMs respectively. This study predicts a human MTD of 1145 microg/m2. The reported human MTD of ET-743 given as a 24-h continuous infusion every 3 weeks is 1800 microg/m2 [J. Clin. Oncol. 19 (2001) 1256]. Since our predicted MTD is within fourfold of the actual MTD (the interspecies variation in tolerated dose due to differences in clearance rates, **metabolism** pathways and infusion rate) the result confirms the profit of the prediction model.

L73 ANSWER 2 OF 11 MEDLINE on STN DUPLICATE 2
AN 2002405965 MEDLINE
DN 22148539 PubMed ID: 12154027
TI Hepatobiliary damage and changes in hepatic gene expression caused by the

antitumor drug ecteinascidin-743 (ET-743) in the female rat.
AU Donald Sarah; Verschoyle Richard D; Edwards Richard; Judah David J; Davies Reginald; Riley Joan; Dinsdale David; Lopez Lazaro Luis; Smith Andrew G; Gant Timothy W; Greaves Peter; Gescher Andreas J
CS Department of Oncology, University of Leicester, Leicester LE1 9HN, United Kingdom.
SO CANCER RESEARCH, (2002 Aug 1) 62 (15) 4256-62.
Journal code: 2984705R. ISSN: 0008-5472.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200209
ED Entered STN: 20020806
Last Updated on STN: 20020912
Entered Medline: 20020911
AB **Ecteinascidin**-743 (ET-743) is a novel marine-derived anticancer drug with clinical activity in soft tissue sarcoma and ovarian cancer. Reversible transaminitis and subclinical cholangitis have frequently been described in patients who receive ET-743. To facilitate understanding of this adverse effect and help design suitable therapeutic rescue strategies, we characterized the hepatic effects of ET-743 in rats. Female rats received ET-743 (single dose, 40 microg/kg) i.v., and liver changes were assessed from 6 h up to 3 months after dosing by histopathology, immunohistochemistry, electron microscopy, hepatic and plasma biochemistry, and DNA microarray analysis. At 24 h posttreatment and beyond, livers displayed degeneration and patchy focal necrosis of bile duct epithelial cells associated with mild inflammation followed by fibrosis. Sporadic and focal zones of hepatic necrosis and hemorrhage were observed from day 2 onward, although the majority of hepatocytes appeared normal as judged by electron microscopy. Pathological alterations persisted up to 3 months after dosing. Plasma levels of total bilirubin were elevated up to 7-fold over those in untreated rats from day 2 onward and returned to control values by day 24. Activities of alkaline phosphatase and aspartate aminotransferase in plasma were elevated for 2 and 3 months, respectively. Activities of the hepatic microsomal drug-**metabolizing** enzymes cytochrome P-450 A1/2, CYP2E1, and CYP3A2 were decreased. DNA microarray analysis of livers from ET-743-treated animals showed a dramatic increase in the expression of ATP binding cassette transport genes Abcb1a and Abcb1b, which impart resistance to anticancer drugs, and of Cdc2a and Ccnd1, the rodent homologues of human cell cycle genes CDC2 and cyclin D1, respectively. The cell cycle gene expression changes mirrored ET-743-induced increases in liver weight and Ki-67 labeling of liver nuclei. The results suggest that the toxicity exerted by ET-743 in the rat liver is a consequence of biliary rather than hepatocellular damage and that it is accompanied by a wave of mitogenic activity, which may be driven by the transcriptional increase in Cdc2a expression.

L73 ANSWER 3 OF 11 MEDLINE on STN DUPLICATE 3
AN 2002482926 MEDLINE
DN 22217442 PubMed ID: 12231541
TI Rat and human liver cytochrome P-450 isoform **metabolism** of **ecteinascidin** 743 does not predict gender-dependent toxicity in humans.
AU Reid Joel M; Kuffel Mary J; Ruben Stacie L; Morales Jose J; Rinehart Kenneth L; Squillace David P; Ames Matthew M
CS Department of Oncology, Division of Developmental Oncology Research, Mayo Clinic, Rochester, Minnesota 55905, USA.
NC N01-CM57200 (NCI)

SO CLINICAL CANCER RESEARCH, (2002 Sep) 8 (9) 2952-62.
Journal code: 9502500. ISSN: 1078-0432.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200211
ED Entered STN: 20020925
Last Updated on STN: 20021213
Entered Medline: 20021104

AB **Ecteinascidin** 743 (ET743, NSC648766) is a marine natural product with potent in vivo activity in human xenograft models. Hepatotoxicity was the most prominent toxicity in preclinical studies and was greater in female rats than in male rats. To assess the potential implications for human toxicities, the in vitro **metabolism** of ET743 was characterized using rat and human preparations. NADPH-dependent ET743 **metabolism** was greater with male rat liver microsomal preparations than with preparations from female rats and was induced by pretreatment of rats with phenobarbital and dexamethasone but not by pretreatment with 3-methylcholanthrene. Rat and human microsomal **metabolism** of ET743 was reduced in the presence of chemical CYP3A inhibitors or antirat CYP3A2 antiserum and to a much lesser extent by CYP2E, CYP2C, and CYP2A inhibitors. In human liver panel studies, ET743 disappearance was highly correlated with CYP3A activities and to a lesser extent with CYP2C activities. ET743 was **metabolized** by a number of cDNA-expressed rat P-450 isoforms, including male-predominant CYP2A2 and CYP3A2. ET743 was **metabolized** by cDNA-expressed human CYP3A4 and to a much lesser extent by CYP2C9, CYP2D6, and CYP2E1 preparations. Three oxidative **metabolites** were detected in cDNA-expressed isoform incubations, including the N-demethylated **metabolite** ET729 and two additional products characterized by laser capture-mass spectrometry analyses. The plasma pharmacokinetics and biliary excretion of ET743 were characterized in rats. There were no gender-dependent differences in half-life or total body clearance values. Although very modest, the biliary excretion of ET743 in male rats (0.48%) was greater than in female rats (0.28%). In contrast, the biliary excretion of the cytotoxic N-demethylated **metabolite** ET729 was 5-fold greater in the female rat (1.05% of dose) than in the male rat (0.19% of dose). Biliary excretion of ET729 may contribute to the hepatic toxicity in rats. These data are consistent with a major role for CYP3A isoforms in ET743 rat and human **metabolism**. Although there are conflicting data in the literature, expression of CYP3A isoforms in human tissues and elimination of CYP3A substrates have not been shown to vary substantially by gender. There are no indications that the other CYP isoforms implicated in ET743 **metabolism** are expressed differently in males and females. Thus, although it is not possible to rule out gender differences in ET743 human toxicities, our data do not predict major gender-dependent differences in the toxicity of ET743 based on **metabolism**.

L73 ANSWER 4 OF 11 MEDLINE on STN DUPLICATE 4
AN 2002495269 MEDLINE
DN 22243844 PubMed ID: 12357306
TI Pharmacokinetics of ecteinascidin 743 administered as a 24-h continuous intravenous infusion to adult patients with soft tissue sarcomas: associations with clinical characteristics, pathophysiological variables and toxicity.
AU Puchalski Thomas A; Ryan David P; Garcia-Carbonero Rocio; Demetri George D; Butkiewicz Leah; Harmon David; Seiden Michael V; Maki Robert G; Lopez-Lazaro Luis; Jimeno Jose; Guzman Cecilia; Supko Jeffrey G
CS Dana-Farber/Partners Cancer Care, Harvard Medical School, Boston,

Massachusetts, USA.
SO CANCER CHEMOTHERAPY AND PHARMACOLOGY, (2002 Oct) 50 (4) 309-19.
Journal code: 7806519. ISSN: 0344-5704.
CY Germany: Germany, Federal Republic of
DT (CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE II)
Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200211
ED Entered STN: 20021002
Last Updated on STN: 20030105
Entered Medline: 20021122

AB PURPOSE: **Ecteinascidin** 743 (ET-743) is a potent cytotoxic alkaloid of marine origin that has shown promising evidence of antitumor activity during phase I clinical trials. In the study reported here, the influence of clinical characteristics and pretreatment pathophysiological variables on the pharmacokinetics of ET-743 and their associations with drug-related toxicity was examined in sarcoma patients treated in three phase II clinical trials. METHODS: Adult patients with various histological subtypes of soft tissue sarcoma received 1.5 mg/m(2) of ET-743 by 24-h continuous i.v. infusion once every 3 weeks. Eligibility criteria were similar for each study, except for the histological subtype of the tumor or the extent of prior treatment with other anticancer agents, and all patients had normal or near-normal liver and renal function. The maximum plasma concentration (C(max)) and area under the plasma profile from time zero to infinity (AUC) of the drug were determined during the first cycle of therapy. Patients were evaluated for toxicity every week. RESULTS: Geometric mean +/- SD values of the pharmacokinetic parameters in 69 patients were: C(max) 1.14 +/- 0.52 ng/ml, AUC 39.9 +/- 16.6 ng.h/ml, and total body clearance (CL) 36.7 +/- 16.4 l/h per m(2). The only significant correlation involving physical characteristics of the patients or pretreatment pathophysiological variables was a very weak relationship between alkaline phosphatase and AUC ($r=0.39$, $P<0.01$). The 15 patients with any baseline liver function test exceeding the upper limit of the normal ranges had a significantly greater ($P=0.02$) incidence of severe toxicity (80% vs 44%). Although the mean AUC of ET-743 in patients with elevated serum levels of hepatic enzymes was 17% greater than that in patients with normal pretreatment liver function tests, the difference was not significant ($P=0.22$). In addition, there was no distinct relationship between the grade of the most severe drug-related toxicity that occurred during the first cycle of therapy and the AUC for the entire cohort. The CL of ET-743 was found to be 27% greater in patients concurrently receiving dexamethasone as a preventative antiemetic than in those who were not, but the difference did not achieve statistical significance ($P=0.08$). There were no significant associations between CL (liters per hour) and body surface area or any other variable related to body size. CONCLUSIONS: The risk of developing severe toxicity was substantially enhanced in patients with relatively moderate indications of hepatic dysfunction without a coincident effect on the CL of ET-743. Dexamethasone cotreatment appeared to decrease the incidence of severe toxicity as well as the AUC of the drug. Delivering a fixed amount of drug without adjustment for the height or weight of the patient may be more appropriate than dose normalization due to the absence of an association between CL and body surface area. Optimizing dosing strategies to further enhance the therapeutic index of ET-743 may depend upon obtaining a better understanding of the **metabolic** fate of the drug in humans.

L73 ANSWER 5 OF 11 MEDLINE on STN DUPLICATE 5

AN 2001697942 MEDLINE
DN 21610540 PubMed ID: 11744617
TI A pharmacophore for human pregnane X receptor ligands.
AU Ekins Sean; Erickson Jon A
CS Lilly Research Laboratories, Eli Lilly and Company, Lilly Corporate Center, Drop Code 0730, Indianapolis, IN 46285, USA.. ekins_sean@lilly.com
SO DRUG METABOLISM AND DISPOSITION, (2002 Jan) 30 (1) 96-9.
Journal code: 9421550. ISSN: 0090-9556.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200202
ED Entered STN: 20011218
Last Updated on STN: 20020207
Entered Medline: 20020206
AB The pregnane X receptor (PXR) is involved in transcriptional regulation of multiple cytochromes P450 and multidrug resistance-associated protein (MDR1), which encodes for the drug transporter P-glycoprotein. Crystal structure analyses suggest that the ligand binding domain is highly hydrophobic and flexible, allowing molecules of differing sizes to bind in multiple orientations. Using literature data for EC(50) (half-maximal inhibitory concentration) values for PXR activation derived for 12 human PXR ligands, a pharmacophore was developed. This pharmacophore supports the hydrophobic nature of the ligand binding domain recently deduced from the X-ray crystal structure because it contains four hydrophobic regions and one hydrogen bond acceptor. These features are consistent with at least one of the three experimentally determined orientations in which SR12813 binds to PXR, as determined by overlay studies. SR12813 fulfills all of the five pharmacophore features, as does the potent ligand hyperforin. The pharmacophore was also used to predict the binding affinity for 28 molecules not in the model but known to be PXR ligands of differing potencies. The pharmacophore distinguished the most potent activators of PXR (that display >5-fold activation/deactivation), like **ecteinascidin**, troglitazone, nifedipine, and dexamethasone-t-butylacetate, from poor activators, such as scopoletin and kaempferol. The model could be useful in drug development, potentially acting as a high-throughput filter for identifying compounds that may bind to PXR before in vitro determination. Ultimately, this will aid in the selection of molecules with a lesser capacity to be potent PXR ligands and thus avoid induction of numerous drug-**metabolizing** enzymes and MDR1.

L73 ANSWER 6 OF 11 MEDLINE on STN DUPLICATE 6
AN 2001562366 MEDLINE
DN 21489910 PubMed ID: 11604552
TI Search for **metabolites** of **ecteinascidin** 743, a novel, marine-derived, anti-cancer agent, in man.
AU Sparidans R W; Rosing H; Hillebrand M J; Lopez-Lazaro L; Jimeno J M; Manzanares I; van Kesteren C; Cvitkovic E; van Oosterom A T; Schellens J H; Beijnen J H
CS Faculty of Pharmacy, Department of Biomedical Analysis, Division of Drug Toxicology, Utrecht University, 3584 CA Utrecht, The Netherlands.. R.W.Sparidans@pharm.uu.nl
SO ANTI-CANCER DRUGS, (2001 Sep) 12 (8) 653-66.
Journal code: 9100823. ISSN: 0959-4973.
CY England: United Kingdom
DT (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals

EM 200112
ED Entered STN: 20011022
Last Updated on STN: 20020122
Entered Medline: 20011207
AB **Ecteinascidin** 743 (ET-743) is a potent anti-tumoral agent of a marine origin. It is currently being tested in phase II clinical trials using a 3-weekly 24-h i.v. infusion of 1500 microg/m(2) and 3-h infusions of 1650 microg/m(2). Knowledge of the **metabolism** of ET-743 is, however, still scarce. In the present study, a qualitative chromatographic discovery of **metabolites** of ET-743 in man is reported. ET-743 and its demethylated analog ET-729 were incubated at 37 degrees C in the presence of enzyme systems, pooled human microsomes, pooled human plasma and uridine 5'-diphosphoglucuronyltransferase, respectively, in appropriate media. Reaction products were investigated chromatographically using photodiode array and ion spray-mass spectrometric detection (LC-MS). The main reaction products in microsomal incubations of ET-743 resulted from a remarkable breakdown of the molecule. In plasma the drugs were deacetylated, and the transferase did actually yield a glucuronide of both ET-743 and ET-729. In contrast, screening of urine, plasma and bile, collected from patients treated with ET-743 at the highest dose levels, using a sensitive LC-MS assay, did not result in detection of ET-729 and **metabolites** which were generated in vitro. The urinary excretion of ET-743 in man was lower than 0.7% of the administered dose for a 24-h infusion.

L73 ANSWER 7 OF 11 MEDLINE on STN
AN 2003527470 IN-PROCESS
DN PubMed ID: 14604355
TI Synthesis of natural ecteinascidins (ET-729, ET-745, ET-759B, ET-736, ET-637, ET-594) from cyanosafracin B.
AU Menchaca Roberto; Martinez Valentin; Rodriguez Alberto; Rodriguez Natividad; Flores Maria; Gallego Pilar; Manzanares Ignacio; Cuevas Carmen
CS Pharma Mar, S. A. C/Avda de los Reyes, 1.P.I. La Mina-Norte. 28770 Colmenar Viejo, Madrid, Spain.
SO Journal of organic chemistry, (2003 Nov 14) 68 (23) 8859-66.
Journal code: 2985193R. ISSN: 0022-3263.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS IN-PROCESS; NONINDEXED; Priority Journals
ED Entered STN: 20031108
Last Updated on STN: 20031219
AB The semisynthetic process initially described for the synthesis of 1 (ET-743) has been extended to the preparation of other natural **ecteinascidins**. For the synthesis of 2 (ET-729) a demethylation of a N-**Me** intermediate was carried out by a selective oxidation with MCPBA. Other natural **ecteinascidins** (ET-745, ET-759B, ET-736, ET-637, ET-594) were accessible from key intermediate 25. The described methodologies allow for the preparation of a wide variety of **ecteinascidins** by procedures that can be easily scaled up.

L73 ANSWER 8 OF 11 MEDLINE on STN
AN 2003468551 MEDLINE
DN PubMed ID: 14529519
TI Drugs from the sea: conotoxins as drug leads for neuropathic pain and other neurological conditions.
AU Alonso D; Khalil Z; Satkunanthan N; Livett B G
CS NeuroPharma, S.A.; Avda. de la Industria 52, 28760 Tres Cantos, Madrid, Spain.. dalonso@neuropharma.es
SO Mini reviews in medicinal chemistry, (2003 Nov) 3 (7) 785-7. Ref: 37

Journal code: 101094212. ISSN: 1389-5575.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200311
ED Entered STN: 20031008
Last Updated on STN: 20031218
Entered Medline: 20031121

AB The oceans are a source of a large group of structurally unique natural products that are mainly found in invertebrates such as sponges, tunicates, bryozoans, and molluscs. It is interesting to note that the majority of marine compounds currently in clinical trials or under preclinical evaluation are produced by these species rather than as secondary **metabolites** by marine algae. Through the combined efforts of marine natural products chemists and pharmacologists a number of promising compounds have been identified that are either already at advanced stages of clinical trials such as the new anti-cancer drug marine alkaloid **ecteinascidin** 743, or have been selected as promising candidates for extended preclinical evaluation. This is the case for conotoxins, (Table 1) where a number of conopeptides are currently being developed as analgesics for the treatment of neuropathic pain.

L73 ANSWER 9 OF 11 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AN 2002:225572 BIOSIS
DN PREV200200225572
TI **ETM-775 metabolite** of **ecteinascidin** 743.

AU Rinehart, Kenneth L. [Inventor]; Morales, Jose J. [Inventor, Reprint author]; Reid, Joel [Inventor]; Reymundo, Isabel [Inventor]; Floriano, Pablo [Inventor]; Gravalos, Lola Garcia [Inventor]
CS Urbana, IL, USA
ASSIGNEE: The Board of Trustees of the University of Illinois

PI US 6316214 November 13, 2001
SO Official Gazette of the United States Patent and Trademark Office Patents, (Nov. 13, 2001) Vol. 1252, No. 2. http://www.uspto.gov/web/menu/patdata.html. e-file.
CODEN: OGUPE7. ISSN: 0098-1133.
DT Patent
LA English
ED Entered STN: 3 Apr 2002
Last Updated on STN: 3 Apr 2002

AB The purification and structure elucidation of several products of the **metabolism** of Et 743 by human cytochrome CYP3A4 have been accomplished. These compounds are abbreviated herein as "ETM" followed by a numeric value, which represents the approximate molecular weight. Three compounds have been identified to date, namely **ETM 305**, **ETM 775** and **ETM 204**. The structures of these **ecteinascidin metabolites** are as follows: ##STR1##

L73 ANSWER 10 OF 11 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AN 2001:468851 BIOSIS
DN PREV200100468851
TI Search for **metabolites** of **Ecteinascidin**-743 (Et-743), a novel marine derived anticancer agent.

AU Beijnen, Jos H. [Reprint author]; Rosing, Hilde; Sparidans, Rolf; Hillebrand, Michel; Lopez-Lazaro, Luis; Jimeno, Jose; Cvitkovic, Esteban;

Van Oosterom, Alan; Schellens, Jan
CS Paul Brousse Hospital, Villejuif, France
SO Proceedings of the American Association for Cancer Research Annual Meeting, (March, 2001) Vol. 42, pp. 545. print.
Meeting Info.: 92nd Annual Meeting of the American Association for Cancer Research. New Orleans, LA, USA. March 24-28, 2001.
ISSN: 0197-016X.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 3 Oct 2001
Last Updated on STN: 23 Feb 2002

L73 ANSWER 11 OF 11 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AN 1997:234199 BIOSIS
DN PREV199799533402
TI Cytochrome P450 catalyzed **metabolism** of **Ecteinascidin** 743 by rat and human liver microsomes.
AU Kuffel, M. J.; Reid, J. M.; Ames, M. M.
CS Mayo Clinic, Rochester, MN 55905, USA
SO Proceedings of the American Association for Cancer Research Annual Meeting, (1997) Vol. 38, No. 0, pp. 596.
Meeting Info.: Eighty-eighth Annual Meeting of the American Association for Cancer Research. San Diego, California, USA. April 12-16, 1997.
ISSN: 0197-016X.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 2 Jun 1997
Last Updated on STN: 9 Jul 1997

=> log h